

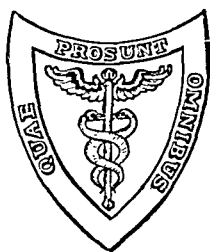
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JANUARY, 1939

ORIGINAL ARTICLES.

THE "ROMANTIC" ATTRIBUTES OF "LAWLESSNESS" AND
"MALIGNANCY" IN CANCER.

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I PROPOSE to consider here briefly two of the generally accepted characteristics of cancer growth: (1) its so-called lawlessness and, (2) its malignant aggressive behavior.

1. We are told very generally in textbooks of pathology that cancer cells are lawless, that they grow wildly, contrary to all rules, without correlation, are without meaning, that they are wolves in sheep's clothing; in short, the gangsters of the body. At the outset it may be said that such views at once renounce all intelligibility of cancer growth. They thus violate the logical standpoint of causality of a natural phenomenon. In other words, the statement that cancerous growth, though atypical, is lawless, separates it from all other biologic phenomena and thus puts it beyond understanding. Such a conception, however, may not be tolerated under any pretence in any scientific inquiry, even under the cloak of a "heuristic" principle; for no matter how simply we may want to describe a natural event to the uninformed, it will never do to put it beyond natural laws or order. It is a necessary logical principle of all scientific inquiry that in Nature nothing occurs without a lawful causal chain, whether it fits into the normal scheme or whether it lies outside of it. The destructive lightning which may kill, the frightful eruptions of a volcano annihilating thousands of individuals at one time, are in fact just as lawful natural events as others which happen to support mankind and to please its self-preservation. Indeed, this consideration of causality must in the

last instance also apply to a scientific inquiry into cancer and cancer growth. The first requisite, therefore, is to find if possible the laws or order of its manner of growth. To dismiss this fundamental point with a brief statement that (contrary to all other natural phenomena) cancer stands (like a miracle) purely by itself and to deny it any law and order, defeats at once the very possibility of its understanding. Indeed, this happens often enough in present cancer research which has centered (with few exceptions) almost entirely around etiologic factors. It has thus shifted the cancer problem to an entirely false position, without proper regard to the main point of its nature. It is to be regretted that this distorted standpoint is becoming uppermost even in the minds of pathologic anatomists, who are apt to leap over this side of the cancer problem. If then, on purely *a priori* logical ground, we should hesitate to accept this conception of lawlessness of a natural phenomenon, we are at once confronted by the question: Are there any real demonstrable facts at our disposal which may lead us to a better understanding of cancerous growth, or must we confess that we are, at least at present, quite unable to detect in cancer anything which points to a consistent and definite plan in manner of growth? For it may confidently be expected that if such observations exist, they will open up the right path for the approach to the cancer problem and show us the way to follow in unfolding it. Such observations are available and have now reached a point where their more general appreciation is ripe and necessary.

Every pathologic anatomist who has observed early cancerous growth, especially in glandular organs as in the gastro-intestinal tract, will have been impressed by the fact that the growth and extensions of cancer cells follow primarily the normal prescribed arrangement of glandular construction. Thus cancer cells and the so-called tumor "autonomy" do not declare themselves independent from normal tissues at once. The earlier investigators into the cancer growth were well aware of this and have given good descriptions and illustrations of this step of cancerous progress. For example, Ribbert as well as Borst have repeatedly described and illustrated such pictures in detail and these observations have been confirmed by others in earliest cancer growth (Versé, Böhmig). One may see here quite commonly a simple substitution of normal glandular epithelium by cancer cells which follow this architectural arrangement, so that normal tubules and acini are gradually lined by cancer cells. At this stage basement membranes are not broken but normal cells are simply lifted off by cancer cells and atrophy; the tubular lumen remains clear and the whole architectural plan of glandular tissue is preserved. Böhmig has, in quite recent convincing studies, reëmphasized this fact and also that the penetration of cancer into the deeper parts of the mucous membrane and muscularis mucosæ occurs only after the occupation of normal

glands is completed. Cancer cell growth is, therefore, at the start integrated with normal structure. I saw this years ago (1907) in the primary cancer of the liver in which, as I pointed out, cancer cells still may enter into the construction of the lobule. I stated "these (cancer) cells still entered at that time into the construction of the lobule, and showed the arrangement in rows after their individual change in cell character had occurred and no disturbance in the lobule had taken place; ample proof that these small islands were not metastases, but primary cancerous foci." It was only after these cells began to reproduce that they broke with the former arrangement and structure. I called this the incipient stage of a "cancerous" cell regeneration. Böhmig recognizes this recently as the first phase of cancer development.

Even the subsequent substitution of normal epithelium by glandular cancer cells is not particularly specific, for it occurs by other non-cancerous types, and may be observed elsewhere. Thus Homma points out the occasional substitution of mucoid epithelium by normal squamous epithelium in erosions of the cervix. Marpurgo reports replacement of epithelium in the mucous glands in the cervical canal by non-cancerous epithelium of the vaginal cervical lining. Similar observations by others have shown that in all such instances of tumor or non-tumor cell replacements, the *intensity of growth* of one kind of epithelium supersedes and replaces that of the other. Cell substitution is therefore the expression of the intensity or of the tempo of growth. Now with the continuation of the same intensity of growth there appears, after the occupation of original normal glandular tubules is finished, a necessary change in their arrangement and space occupation; that is, a renewed formation of new, now cancerous tubules and acini. But even in this second, complete cancerous phase, Böhmig was able to demonstrate that the plan of normal glandular development as laid down by Heidenhain—that is, tubular (dichotomous) division with formation of dimeres, acini, and adventitial appended glandular buds and sympodia*—is maintained throughout. The *apparently lawless growth* may therefore be reduced to that of *intensity or increased tempo of growth*, while still proceeding within the lawful order of all other glandular formations.

Böhmig has also shown by systematic studies of series of cases that the subsequent environment into which the cancerous tissue moves has a decided influence on its subsequent manner (differentiation) and intensity of growth, a fact generally well known to most pathologic anatomists. Thus growth in submucosa and subserosa is more abundant and completely differentiated than in the muscular coat. The latter shows an inhibition in number and form

* When one of the dichotomous daughter buds is forced to one side and is thus retarded in further growth, there results a "sympodial type," normally exhibited in the development of the pancreas (Neubert and Heidenhain).

of growth associated with a diminution in differentiation and thus the formation to simpler epithelial structures. In mammary cancer, Böhmig found the quantity of growth and its differentiation better and greater in the glandular lobules of the breast and within the adjoining fat tissue but decidedly restricted and abbreviated in the collagenous fibers of the stroma. Similar observations were made by him in papillary cancers. He concludes that there is a considerable influence on the manner of growth by what Heidenhain terms "the limiting function of the formative area." This suppression of quantity of growth and differentiation may be removed once more when the tumor passes on to other favorable formative fields and the former scheme and manner of growth reassert themselves. One finds this illustrated in cancers of mucous membranes (stomach, gut) which after having penetrated and extended in the submucosa for a distance, reënter the mucosa from below and replace the normal glandular cells of tubules in a new focus, imitating renewed cancer development. Ribbert and Borst have repeatedly found such illustrations. Even here the scheme of renewed growth in an original environment follows Heidenhain's laws in the unfolding of form and tissue arrangement.

This discovery appears to be of great consequence in the fate of cancers and their general behavior. Böhmig concludes that the original or acquired structural peculiarities of the environment determine to a large extent the degree of differentiation and manner of growth in the cancerous extensions and metastases. Thus a more typical adenocarcinoma occurs only in organs or tissues which structurally permit the development of a glandular scheme. If this structural environment has been altered by processes of age or by irritative or regressive tissue changes, it becomes unsuited for the development of new glandular growths. Differentiation and manner of growth are then lowered or checked. Thus also an already established glandular cancer may in its advance into new tissues change its type and manner of growth to that of a scirrhus.

It is for these reasons quite impossible to "grade malignancy" by the type of cell occurring in a particular locality for, just as in Heidenhain's laws of normal tissue development, the realization of growth in cancers is a combination of "Anlage" and environment under which cells operate. In this regard the constant interacting local reciprocal play between advancing cancer parenchyma, stroma, vessels and nerves, assumes quite a new and important aspect. Indeed, upon presence or absence of this play depends the cancer "take" or formation of the actual cancerous tumor, the possibility of its extensions and metastases. I have emphasized this importance in a number of previous publications.

The structural development of metastases demonstrates a similar order of things except that the first phase of structural adaptation to the original is omitted. But Heidenhain's law of sequence of

glandular formation to tubular dichotomous division (dimeres) and to adventitial buds and sympodial growth, is generally followed no matter in what organ or tissue metastasis occurs, unless the structural peculiarities of the new seat prevent this complete unfolding. In all instances, primary or secondary cancer growth is, therefore, directed, not lawless. These observations are, as Böhmig points out, still further supported by the constancy in the distances of tubular division of first and second order, and in size of lumina and epithelial linings of cancerous tubules, unless the new seats of growth have been subject to previous changes which will, as stated above, reflect on the tumor development.

The conclusions of these numerous observations, which have been well collected and analyzed by Böhmig, are plain: The cancerous growth is not a lawless, uncontrolled growth. It follows the general laws of development which have been laid down by Heidenhain for normal conditions. They are also open to the modifications of its environment, principally through "limitations of formative space," just as in normal differentiation. *All these features of cancer growth may therefore be reduced to one basic fact, that is, intensity or tempo of growth.* The latter is a problem into which we need not enter here as we are concerned only with the lawful order of development which characterizes cancer cells in their growth. Years ago Billroth stated that scientifically speaking there was no such thing as a special tumor problem, but only one of typical and atypical growth, and he intimated that as soon as we know more of the plans of typical growth, the atypical would naturally fall into its place. He saw this with an almost prophetic vision, for the subsequent discovery of the normal laws of growth by Heidenhain appear now plainly applicable to cancerous growths. Thus the understanding of the normal has opened the door to the understanding of the abnormal. These considerations lead directly to the second point, that of "malignancy" or "aggression" of cancer cells.

2. We are commonly told that cancer cells are aggressive, malignant. They have even been compared to gangsters. What does this really mean in sober language? Do they possess specific properties which other proliferating, moving and accumulating body cells do not possess? May they bring about a direct cancerous attack on tissues? I have had this phase of the cancer problem under study for a number of years and come to the conclusion that such specific cancerous attributes do not exist, but that these so-called malignant properties may be reduced to purely quantitative measures. I voiced this in a previous publication (1935) in the following words: "Is there really such a thing as an "aggressive" character in "malignant" tumor cells? Based on this and on some previous observations, I think this may well be doubted. It may perhaps be reduced to matters of relative nutrition and freedom of movement. The arrested, actively growing, mobile tumor cells hold,

by virtue of their primary (blood or lymph) vascular position, the first call on the nutritive material. It does not seem to me necessary to assume "specific" food substances. The withdrawal of most of the nutritive material and the local circulatory modifications caused by the presence of these growing and multiplying cells in the circulatory tracts, permit them to expand and encroach upon the stationary, wasting parenchyma. Thus an ever-widening cancerous circle and influence are established."

I had arrived at this conclusion in the study of sarcomatous as well as carcinomatous progress within other fixed tissues, for example, liver, muscle and lymph glands, in which their invasion and future progress may be readily followed. Here it could be shown that the so-called infiltrative (malignant) capacity of the tumor cells was in reality only an intracanalicular vascular advance which finally ended in tissue spaces and became intercellular and interfibrillar. There was nowhere any evidence that these fixed tissue cells were exposed to any particular "killer" action by cancer cells. Waste of tissue cells and fibers occur purely by nutritive atrophy as results of greater quantitative measures of tumor growth. Their presence within the nutritive and tissue channels of the locality interfere, of course, with the proper circulatory movements and nutrient exchange between blood, tissue fluids and tissue cells. The intervening tumor cells have first call on this nutrient material and its supply is withdrawn by them before it may come into contact with fixed tissues. To this comes the occupational pressure by the actively proliferating formative cancer parenchyma. Böhmig has quite recently (1937) made similar observations in adenocarcinomatous metastases of the liver from which he concludes that, first, solid epithelial plugs push their way forward in the lobular venules and, secondly; they lead through the formation of glandular loops to atrophy and waste of adjoining liver columns. Nowhere appeared, even to him, any specific direct aggression on liver cells, and cancerous advance is throughout all organs intracanalicular. The result is here quite similar to what occurs in these organs in other pathologic occupations of longer standing (blood congestion, exudates, non-irritating foreign material). All of these lead to quantitative disturbances and relations in the occupied areas and waste of fixed tissues. We therefore arrive at a conclusion similar to that as regards lawfulness of tumor growth: *Malignancy is also reducible to terms of intensity or tempo of growth.*

I have dealt in these lines—it must be fully understood—only with two of the important characteristics of cancerous growth. It has not been the intention to go further into the other issues of the cancer problem. What I was anxious to show was simply that if we really wish to arrive at a better understanding of cancer growth (and we must do so before we can really go much further with it, except by shots in the dark), we must get rid of all those "romantic"

ideas into which cancer investigation has fallen and in which it will completely drown unless it is once more rescued from popularization and treated purely as a problem of growth; not "*sub specie individualitatis*," but "*aeternitatis*." These observations indicate that such a route is possible and worthwhile. I hope also that they reëmphasize the still great necessity of structural investigation of cancer in relation to its environmental determinants. Kreyberg's illuminating observations on the structural changes leading to cancer formation after tarring mark here a substantial progress in the understanding of cancerous development.

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LOCALIZATION OF CARDIAC INFARCTS IN MAN.

I. A COMPARISON OF ANTERIOR-POSTERIOR WITH MUSCLE BUNDLE MODES OF LOCALIZATION.*†

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AMONG the most rapidly developing chapters of medicine is that of coronary disease. The first combined clinical and electrocardiographic study published by Herrick¹⁵ in 1919 has been followed by a world wide flow of publications. White³³ lists 56 papers which are only a fraction of those available.

Antemortem localization by means of the electrocardiogram was at one time not considered possible.^{10,14,17} More recently there is a countertrend and multiple diagnostic criteria have evolved for which a measure of efficiency is claimed. An impetus to the latter group was derived from the observations of Parkinson and Bedford,²⁰

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whose report was based on a study of 26 patients among whom were 6 deaths with 4 autopsies. A quotation from their article indicates the source of the T_1 , T_3 terminology:

"Usually a definite sequence of changes in the R - T segment and in the T waves is recorded. Shortly after the onset of symptoms a transient deviation of the R - T segment occurs. This is followed by a deep inversion of the T wave in either Lead I or III but not in both, and often by a lesser inversion in Lead II. Curves obtained after a few weeks conform to one of two main types according to the incidence of T inversion in Leads I or III" (p. 204). "As a rule the R - T deviation is best seen in Leads I and III and is then constantly in opposite directions in these two leads; thus an R - T elevation in Lead I is associated with an R - T depression in Lead III and *vice versa*. Elevation in Lead I is about as frequent as depression in Lead I, . . . R - T deviation may, however, be confined to a single lead (Figs. 16, 27) or may be most evident in Leads I and II or Leads II and III."

Barnes and Whitten,⁶ using the T_1 , T_3 terminology, analyzed a series of 47 case histories with autopsies, 12 selected for detailed report. That it is not always easy or even possible to classify tracings as Type T_1 or T_3 is evidenced by the following quotation: "Elevation or rounding of the contour of the R - T segments in Leads I and II will serve to identify the abnormality as Type T_1 although no inversion of T is present (p. 149). Occasionally in Lead I the identification of an abnormality of Type T_1 depends on an inverted T wave in the lead with R - T characteristics preceding it which suggest infarction [p. 149]. . . . In the light of these observations we have classified our electrocardiograms into Types T_1 and T_3 and have subdivided these types into groups listed as typical, less typical, and indeterminate (p. 150)."

Crawford, Roberts *et al.*⁹ showed experimentally in cats that lesions by cautery on the anterior surface of the left ventricle gave a T_1 type of electrocardiogram, those over the posterior surface and apex gave a T_3 type. Those over the whole right ventricle except the base anteriorly gave a T_3 type. They mention certain "unusual" curves and in Figure 6 *A* and *B* reproduce examples which do not fit into the classification, *i. e.*, R - T_1 and R - T_3 are not reciprocal.

Wolferth and Wood³⁵ mention similar trouble and list the confusing factors as: "(1) The infarct may occur in some unusual position, as in the lateral wall of the left ventricle or in the right ventricle. The localizing signs of such lesions are not definitely established as yet. (2) The patient may have had a previous cardiac infarct. (3) Ten cases have occurred in our series of 104 in which contradictory signs have occurred" (p. 77).*

* See also Smith, Goodrich and Needles³⁹ who, in a series of 20 cases with fresh infarcts, found 6 consistent with the actual location, 3 inconsistent and 11 negative or indeterminate.

Büchner, Weber and Haager⁸ also have used the T_1 - T_3 classification. According to them, a coronary T wave in Lead I (in which the R - T may be elevated, depressed, or iso-electric if T_1 is negative) signifies a lesion of the anterior wall of the left ventricle. A similar coronary T wave in Lead III signifies a posterior lesion. A very sharply negative T wave in Leads I or III indicates a long standing lesion.

Robb and her collaborators^{21a, b, 25} have taken cognizance of the existence of the individual muscle bundles in the heart and have demonstrated in 14 dogs and 6 monkeys that injury to any one of these exercises a characteristic effect on the electrocardiogram. If more than one is injured the electrical effects are algebraically summated.

It is the purpose of this essay to illustrate the practical agreement between the topographical (anterior-posterior) and the specific (muscle bundle) modes of localization. This is accomplished first by critical analysis of already published cases and second by descriptions of new cases collected by the authors. Apparent discrepancies might arise from two sources: first, confusion in identifying T_1 and T_3 types and, second, lack of anatomical precision for location of the involved muscles.

A prerequisite for consideration of these sources is an analysis of the statement of Parkinson and Bedford²⁰ that R - T displacement occurs in either Lead I or III but not in both, *i. e.*, R - T_1 and R - T_3 are reciprocal. Records of experimental infarction indicate that this relation is not invariable. Thus Smith³⁰ shows in his Figure 2 an electrocardiogram following ligation of the left anterior descending branch of the left coronary where the R - T is elevated in all three leads (an anterior lesion). Kountz and Hammouda,¹⁸ ligating the same vessel in dog heart-lung preparations, most frequently obtained elevation in all leads. Crawford, Roberts *et al.*⁹ in Figure 6-*A* demonstrate marked elevation in all leads (a posterior lesion). Figure 8-*A* of Barnes and Whitten,⁶ Figure 85-*B* of White,³³ Figure 63 of Wilson in Levy's text,³⁴ Figure 1-*B* of Wolferth and Wood³⁵ are instances of R - T elevation in all leads in man. Depression in all leads may occur; it is shown experimentally in Smith's²⁹ Figure 7 and is also reported by Robb.^{21a} Downward drifting of R - T in all leads in human infarction is seen in Figure 9-*A* of Barnes and Whitten,⁶ and Barnes⁴ reports 7 other cases lacking reciprocal deviation of R - T . These are sufficient examples to establish that the T_1 , T_3 classification is too simple and does not include all the possibilities.

The lack of precision in anatomic localization is also due to overgreat simplification of descriptive terms. There are three functionally separate muscles in the walls of the right ventricle, four in the walls of the left, none of which is limited to any one aspect of either ventricle. Obviously any description of an infarct which omits

either the region on a given surface or the depth of the damaged layer, is, from the anatomist's point of view, inadequate. A brief description of the ventricular muscles* and their blood supply will provide a sound anatomic basis for a correlation between the geographic and the muscle bundle modes of localization. For simplicity's sake, the most common distribution will be stated. An article dealing with variations in distribution is available.²²

A. *The superficial sinospiral muscle* covers most of the base of the right ventricle both anteriorly and posteriorly. It has an origin around the right *A-V* ring and passes downward and forward to form the anterior horn of the left ventricle. There its *second part* plunges deeply to encircle once the apex of the left ventricle; this intramural part contributes the anterior lower third of the septum. In its *third part* it encroaches upon the ventricular cavity as the anterior papillary muscle which is mainly attached to the aortic cusp of the mitral valve. Given that an infarct over the anterior portion of the right ventricle is rare, it follows that most injuries to this muscle are lesions either of the second part in the apical anterior portion of the left ventricle and septum or in the third part, the anterior papillary muscle. The second and third portions are supplied by the distal third (or less) of the anterior descending ramus of the left coronary artery, the first part is supplied by superficial twigs of both the right circumflex and the right lateral branches of the left anterior descending.

Experimental injury to this muscle produces a characteristic change in the electrocardiogram, namely, a moderate elevation of the *R-T* segment in all three leads (expressed as +++), with a concomitant negativity of *T* in all leads. A *T₁* type is the criterion of Barnes and Whitten⁶ for anterior localization. Their Case 3, Figure 8-A, and Figures 1, 3 and 13, of Büchner, Weber and Haager⁸ are instances of *R-T* elevation in all leads with an anterior lesion, located at autopsy, presumably in this muscle. Fowler, Rathe, and Smith¹¹ obtained moderate elevation of *R-T* in all leads when superficial twigs of the coronary branches over the right ventricle were ligated (Fig. 5-B), and when smaller branches to the apical region were ligated (Figs. 1-B and 4-C). In these records *T* is negative in all leads, in the more acute phases.

Vander Veer and Morris³² offer a scholarly review of the electrocardiographic changes in the presence of pericarditis. Diverse explanations of the *R-T* shifts are reported. Some have considered local vessel compression with ischemia (Schwab and Herrmann²⁸ and Feil *et al.*^{10,17}), and others pericarditis (Barnes⁴), to be causative. Wolfert and Wood³⁵ think the elevation in all leads is a summation effect of anterior and posterior infarctions (p. 82). Vander Veer

* Drawings of these muscles appear in the Am. Heart J., 10, 287, 1935, and in the 8th (1938) Ed. of MacLeod's Physiology, p. 268, and therefore need not be shown again here.

and Morris³² believe that an elevation of $R-T$ in all leads, especially in Lead II, along with frequent slurring of the downstroke of R , no change in the chest Lead V, and no well defined Q , are indicative of pericarditis. All their cases with such positive electrocardiograms at autopsy showed definite subepicardial myocarditis. Because this type of record can be obtained as a result of acute infarction in normal hearts, before there is time for pericarditis to develop, it cannot be said to be pathognomonic of pericarditis (Fowler *et al.*,¹¹ Robb^{21a}). On the other hand, pericarditis with myocarditis involving the superficial muscles will give the characteristic records in the absence of infarction (Fig. 5, Part II). The inference is that any conduction interference within a muscle band will affect the electrocardiogram; but (providing similar injury to conducting tissue exists) it will not identify the etiologic agent which produced that change. It has not yet been established that prolonged interference with blood supply due to: *a*, continued external pressure; *b*, progressive sclerosis (or syphilis) with narrowing lumina; *c*, various toxins; or, *d*, slowly developing thrombosis, cause lesions in conducting tissue which differ essentially one from the other. The end result of such interferences with blood supply may well be connective tissue replacement as is also the case following recovery from acute localized myocardial infection. If this be true, the rapidity of change seen in repeated tracings will be the only help which can be expected of the electrocardiogram for differential etiologic diagnosis.⁷ Even this time factor may be misleading if any other pathologic process is fulminating, for then the rapidity of changes will approach those of thrombosis. This will be especially true of thrombosis involving smaller vessels where electrocardiographic changes are less definite and may be slow. If large coronary branches are suddenly occluded, the myocardial lesion and the electrocardiogram are generally specific (see Wilson,³⁴ pp. 281-282). As we have recently been misquoted twice,^{2a, b} let us emphasize that when we speak of conduction "along a muscle band" we are expressing the spatial orientation of the pathway on the surface of the heart without implication concerning the structure which is conducting. Because Purkinje injection techniques have not shown extension into the most superficial layer of muscle such a possibility must be considered. Lewis distinguished between conduction velocity in muscle and in Purkinje tissue, which we have been unable to do; but for this reason we still make reservations (see Robb,^{21a} p. 7, Conclusion 3; Robb *et al.*,²⁶ p. 5; Robb *et al.*,²⁴ p. 6) which is very different from the naive statement that we have "recently admitted the functional activity of the Purkinje network."

B. *The superficial bulbospiral muscle* supplements the sinospiral on the exterior of the ventricles; similarly it has a *second* intramural part, and a *third* part which is commonly known as the inferior (posterior) papillary muscle of the left ventricle. It takes origin by

a small head from the anterior margin of the right *A-V* ring and by a large head from the anterior, left, and posterior margins of the left *A-V* ring. A few fibers may cross the pulmonary conus; the left fibers cover the base of the left ventricle anteriorly, laterally, and

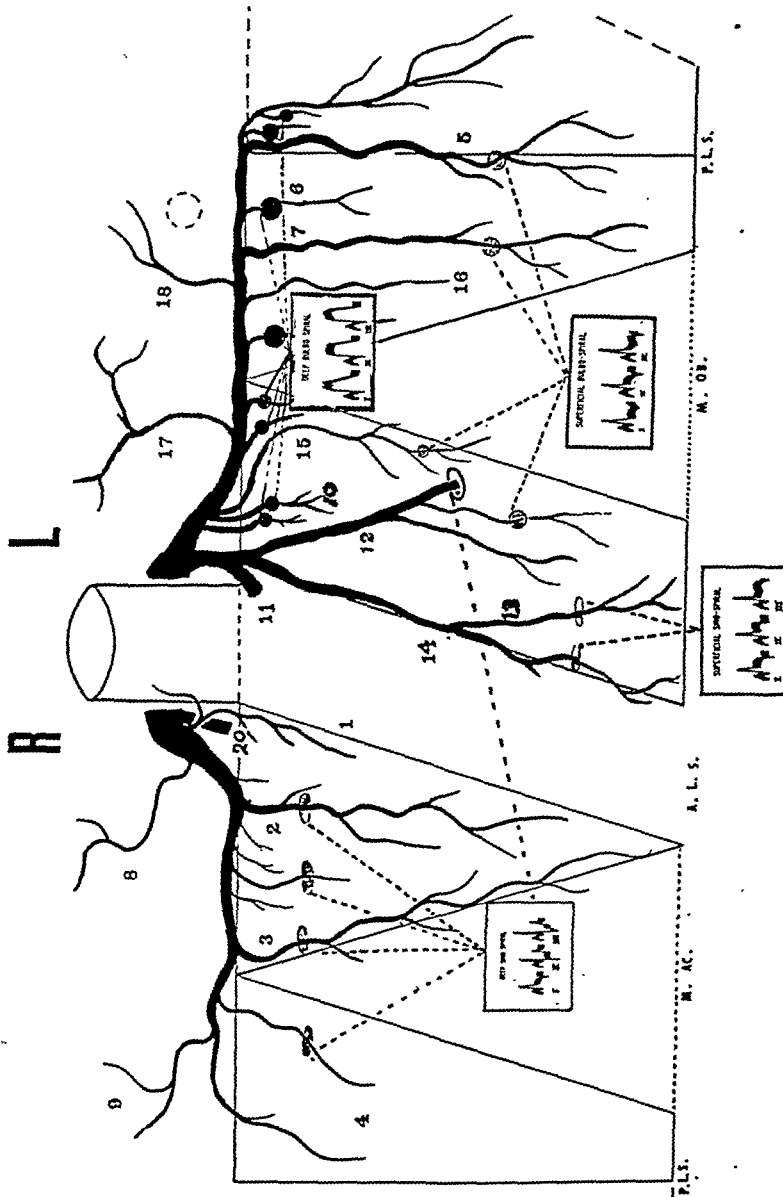


FIG. 1.—Diagram of coronary arteries (modified from Spalteholz text Figure 3) illustrating branches to individual muscles and the electrocardiograms resulting from ligation of those branches. P. L. S. = posterior longitudinal sulcus; M. Ac. = acute margin; A. L. S. = anterior longitudinal sulcus; M. Ob. = obtuse margin. Numbered branches of right coronary artery: 1, Right adipose; 2, right anterior ventricular; 3, right acute marginal; 4, right posterior ventricular; 5, branch to posterior longitudinal sulcus; 6, posterior left ventricular; 7, accessory posterior left ventricular; 8, anterior right atrial; 9, posterior left atrial. Branches of left coronary artery (Nos. 5, 6, 7 from left coronary in 10%): 10, left adipose; 11, septal branch of left anterior descending; 12, 13, first and second collaterals of anterior descending; 14, anterior left ventricular; 15, left obtuse marginal; 16, left posterior ventricular; 17, left anterior atrio-auricular; 18, left posterior atrial branch; 20, superior septal artery (important in animals, often reduced in man, not mentioned by Spalteholz).

posteriorly. It covers the greater part of the diaphragmatic aspect of the left ventricle and the lower (apical) diaphragmatic surface of the right ventricle, giving a few penetrating fibers to the right apex. The fibers converge to form the posterior horn of the left

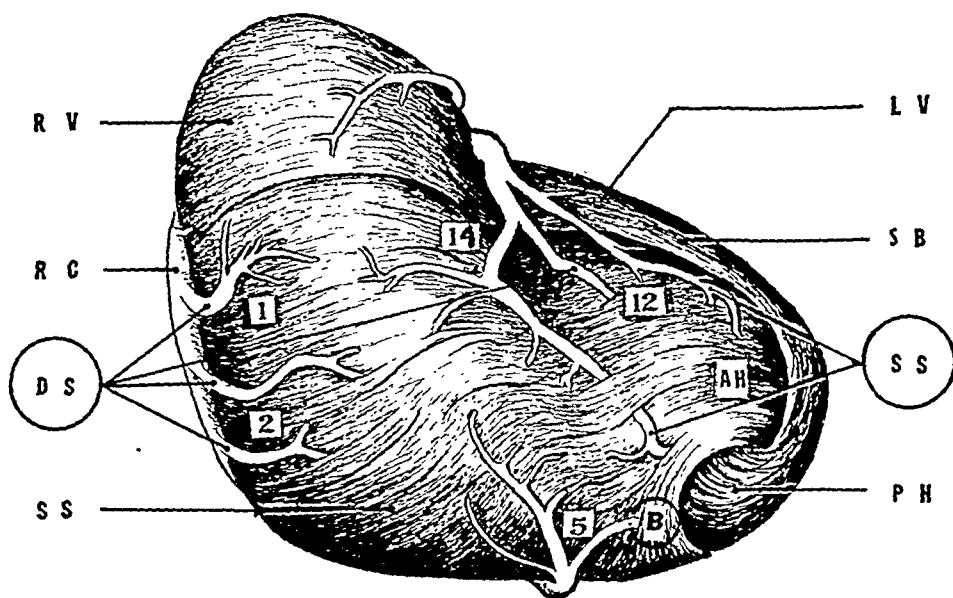


FIG. 2.—Anterior apical view of human heart ($\times \frac{3}{2}$) illustrating the blood supply to individual muscles. R. V. = right ventricle; R. C. = right coronary artery; D. S. = branches of right coronary to deep sinospiral muscle; S. S. = superficial sinospiral muscle and its blood supply; L. V. = left ventricle; S. B. = superficial bulbospiral muscle, and B = its blood supply from the posterior descending artery; P. H. = posterior and A. H. = anterior horn. Arteries numbered as in Fig. 1.

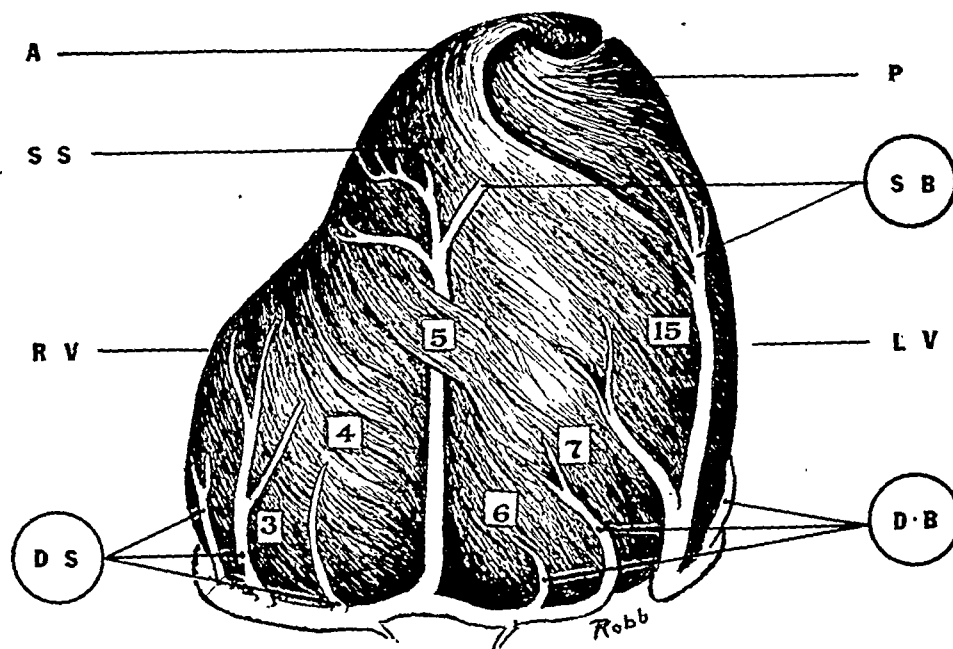


FIG. 3.—Diaphragmatic surface of up-tilted human heart. D. B. = branches from both circumflex arteries supplying the deep bulbospiral muscle. Other legends as before.

ventricle. In its *intramural* course the muscle encircles the apex of the left ventricle once, forming the posterior portion of the lower third of the septum (to which region the superficial sinospiral contributes the anterior portion). The *third* part, which is the inferior (posterior) papillary muscle inserts mainly upon the smaller (inferior) leaf of the mitral valve.

This muscle has a multiple blood supply. The anterior and lateral regions of the first part are supplied by superficial twigs from the several branches of the left circumflex, the fibers at the conus are supplied by twigs either from the first branch of the right circumflex, or from proximal, right lateral, branches of the left anterior descending. The posterior superficial and papillary portions are more often supplied by the right coronary (about 85%), sometimes entirely by the left (5 to 10%) and often in a variable degree by both. The posterior horn also receives a supply from the left anterior descending, via lateral branches just proximal to those supplying the anterior horn; these vessels follow the muscle fiber direction and wind about the apex to enter the base of the papillary muscle. The posterior (inferior) papillary muscle is thus supplied by the left anterior descending, the left circumflex, the right circumflex, or by all three.

Experimentally a lesion in any portion of the muscle results in a characteristic electrocardiogram, *R-T* depression in Lead I and *R-T* elevation in Leads II* and III (-++).

Wilson³⁴ (Fig. 61) reproduces an electrocardiogram of this configuration with the legend "The standard leads show changes characteristic of very recent infarction of the diaphragmatic wall of the heart." Autopsy reports of Büchner, Weber, and Haager⁸ with Figures 5 to 8, and 10 are further instances of lesions presumably in this muscle. Such a record is also presented in Figure 7-C of Barnes and Whitten⁶ for which the autopsy record states: "Infarction involving most of the posterior surface of the left ventricle, the posterior portion of the interventricular septum and one of the papillary muscles was found." Their Figure 6, a photograph of the same heart, shows a posterior papillary lesion, thus verifying the diagnosis of superficial bulbo-spiral infarction. The muscle bundle method of localization would harmonize the apparent discrepancy between their Figures 5-C and 7-C, both presenting depression of *R-T*₁ and elevation of *R-T*₃, in which the former at autopsy exhibited

* The sign of the *S-T* deviation is generally like that in Lead III, occasionally³⁵ the same as in Lead I. In the electrocardiograms obtained in the presence of lesions of a single muscle in experimental animals it was noted that the entire "*S*" wave was involved and not merely the segment from the end of *S* to the beginning of *T*. Especially in small apical anterior lesions of the S.B.S., the *S* is no longer "quick" but becomes a slow deflection. In such small apical lesions of this muscle the slow, thick, shadowed *S* is significant even in the absence of an end-of-*S*-to-*T* depression below the iso-electric level. This observation also proved to be true in human infarction established at autopsy (see especially Fig. 8 of Part II).

an anterior and the latter a posterior lesion. Smith's³⁰ Figure 6 shows this same type of record 2 days after ligation of the right coronary. Otto¹⁹ states that infarctions of the right and anterior portions of the heart (including the basal portion in that region) result in a negative T , and that lesion of the left and posterior portions results in a positive T , and so concludes that the T wave of the intact heart *in situ* reflects disturbances in the balance of electrical activity in the right and left halves of the heart. Here then is real confusion, for while the observations of all agree, the interpretation in one case is of the right *vs.* the left effects, in others, is anterior *vs.* posterior effects. Muscle bundle localization eliminates this conflict since this one muscle is present in all those controversial locations.

Furthermore, if more than one muscle is injured simultaneously, the electrical effect will be the algebraic summation of their individual contributions (Robb,^{21b} Wolferth and Wood,³⁵ p. 82). Accordingly, if both the Superficial Sinospiral effect (+++) and the Superficial Bulbospiral effect (-++) are present the potentials in the Lead I would tend to neutralize each other (unless the electrical effects of one lesion greatly outbalanced the other) and the Leads II and III potentials would tend to be exaggerated. Such interpretation is compatible with the autopsy reports represented by Figures 9-C and 15 of Barnes and Whitten.⁶

C. *The deep bulbospiral muscle* is a strong circular muscle surrounding the mitral orifice and the aorta. In dogs, it is responsible for maintaining pressure in the aorta at the end of systole. When this muscle is injured experimentally the death rate is high, the ventricle fibrillates almost at once. Smith²⁹ (p. 16) produced lesions which must have involved this muscle: (branches of the left circumflex artery, which supply this muscle were ligated). He reports that 4 dogs died during the operation, 4 more died during the night and 6 survived. This mortality is 57%. In our brief series, the death rate was even higher. Legends for Smith's³⁰ Figure 2 and Crawford and Roberts'⁹ Figure 6 make it certain that the deep bulbospiral was involved. The electrocardiograms exhibit the same excessive elevation of $R-T$ in all leads reported by Robb.^{21a} Similar electrocardiograms were obtained by Kountz and Hammouda.¹⁸ During the acute stage the T waves are entirely positive. Three clinical instances (with 2 autopsies) of this type of electrocardiogram have come to my notice. Judging by experimental work, infarcts that would present this picture occur in those individuals who die on the street or elsewhere so abruptly that the electrocardiogram is seldom obtained.

D. *The deep sinospiral muscle* takes origin from the entire circumference of both $A-V$ rings. It encircles both ventricles horizontally, surrounds the basal two-thirds of the left ventricle, lying in the plane between the superficial and deep bulbospiral. It likewise

forms much of the interventricular septum, and is the main mass of both the medial and lateral walls of the right ventricle.

There are two sources of blood supply. The right portion is supplied by all the descending branches of the right circumflex coronary artery. The left portion is supplied from some of the descending twigs of the left circumflex and particularly by the first large left collateral branch of the left anterior descending (this branch may also arise from the very beginning of the left circumflex, or from the bifurcation of the left coronary). The septal portions of this muscle are supplied by the penetrating branches of both the anterior and posterior descending arteries. It is readily seen that occlusion of the proximal portion of the left anterior descending, or the beginning of the left circumflex, or the right circumflex would involve this muscle.

The deep sinospiral has right, left, anterior, posterior, and septal portions: experimental injury to any one of these produces an electrocardiogram characterized by an elevation of $R-T_1$ and a depression of $R-T_3$ (Barnes and Mann,⁵ Harris and Hussey,¹³ and Gross and Calef¹²). In addition, if the septal portion is involved, there is a deep Q (this is also true for the septal portions of the S.S.S., S.B.S., and D.B.S.). Clinically, this type of lesion is common. Crawford, Roberts *et al.*⁹ in Figures 1-B and 2, report the $R-T$ $+ - -$ as an anterior lesion (apex and base). Büchner, Weber, and Haager⁸ in Figures 2 and 4 present instances apparently involving the anterior portion; the septal and posterior portion seems involved in their Figure 11. Barnes and Whitten,⁶ Figure 5-A, also report tracings of the type $+ - -$ in the standard leads with autopsy localization apparently in the posterior portion of this muscle. Parkinson and Bedford²⁰ (Figs. 4a, b, c, 7a, 8, 9) and White³³ (Fig. 84) show this configuration without autopsy support. Summation effects from coincident involvement of other muscles are also common. Probable examples of such occurrence substantiated at autopsy are given by Parkinson and Bedford²⁰ (Case 11, Fig. 12, "thin bulging posterior wall" indicates S.B.S. and D.S.S. involvement; Case 15, Fig. 16, "an old infarction in the septum, anterior wall of the left ventricle, and apex" probably, D.B.S., S.S.S. and S.B.S. respectively). The most frequent combination involves both the S.B.S. and the D.S.S. because they are in extensive juxtaposition with part of their blood supply from a common source. Since the $R-T$ in the characteristic electrocardiogram for the one is $- + +$ and for the other is $+ - -$ it is seen that if there were involvement of each, isoelectric levels might be approached in all leads. When the S.S.S., S.B.S., and D.S.S. are all damaged the $R-T_1$ is usually somewhat elevated and $R-T_3$ is somewhat depressed, also lowered voltage is often seen.

A modification of Spalteholz's³¹ representation of the coronary

system is presented as Figure 1, and sketches of the blood supply to the four ventricular muscles are offered as Figures 2 and 3. It is seen that if the most apical portion of the left anterior descending is occluded, an S.S.S. lesion occurs. If an occlusion is more proximal or if it blocks twigs of Branches 12, 16, or 5, an S.B.S. lesion would result (or both). If the occlusion were still more proximal, anywhere above Branch 12 but still allowing flow in the left circumflex, a D.S.S. lesion would be present, as will also be the case when the right coronary is occluded. Finally, if the smaller descending branches of the left circumflex, the left circumflex itself, or even the whole left coronary be occluded, a deep bulbospiral lesion would be added to the picture. These anatomic facts go far in explaining the discordant results recounted by Gross and Calef.¹² Depending not only on the duration of the lesion but more particularly on the part of the left anterior descending which is occluded, $R-T_1$ may be slightly or very greatly elevated or depressed, $R-T_3$ may be elevated or depressed, and T may be positive or negative. Report of experimental procedures would be more enlightening if ligations were located not by centimeters from the origin of the left anterior descending coronary artery, but rather according to the numbered branches of these vessels (Spalteholz³¹). The distance from the origin may be deceptive, hearts vary much in size, and often the result observed and hence the interpretation depend on the ligature (or occlusion) being above or below a certain branch.

A further agreement between experimental and clinical data is found in the blood pressure measurements. Experimentally D.S.S. lesions are associated with a fall to 80 or 90 mm. Hg systolic pressure (but not the alarming falls noted with D.B.S. lesions). Parkinson and Bedford²⁰ reported large reductions in patients with the D.S.S. type of electrocardiogram (Figs. 4, 8, 9).

This review of the published cases of various authors illustrates the essential agreement between the topographical (anterior and posterior) and the specific (muscle-bundle) methods of localization. Among the cases surveyed, there are no glaring discrepancies, *i. e.*, no anterior or posterior localization which could not equally well be explained by muscle bundle localization. On the other hand, instances are quoted where the muscle bundle localization would reconcile published discrepancies, *e. g.*, right or left, and the "confusing cases" discussed by various authors. The muscle bundle method offers four specific types of electrocardiograms and a basis for analysis of combined lesions whereas the T_1, T_3 method of classification is shown not to include all the commonly found combinations and moreover T_1, T_3 classifications are not necessarily mutually exclusive.

LOCALIZATION OF CARDIAC INFARCTS IN MAN.

II. TWENTY-NINE NEW CASES OF MUSCLE BUNDLE LOCALIZATION
WITH POSTMORTEM CONFIRMATION.*†

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A SUSPICION may arise that the autopsy descriptions previously quoted are not sufficiently exact to warrant muscle bundle localization. Data for 29 cases have been collected which demonstrate that the electrocardiographic localization given for animals is also applicable to man. Also there is evidence that where infarction occurs in an atypical position and where the T_1 , T_2 classification is therefore indefinite, the muscle bundle localization is still definite and applicable.

Superficial Sino-spiral Muscle Lesions (hereafter mentioned as S.S.S.).

CASE 1.—Female, aged 63, admitted with severe pain, 48 hours' duration, 3 hypodermics given. Numbness of left arm, choking sensation. Blood pressure, 144/64. Heart sounds distant, tic-tac, irregular. Later the fibrillation ceased spontaneously. Friction rub present in 4th interspace to left of sternum. Electrocardiograms taken 2 days after the onset of pain showed elevation of $R-T$ in all leads. Seven days later there was a second attack of pain after which the patient gradually failed (Fig. 1). Tachycardia with a pulse deficit preceded death. The moderately enlarged heart came for dissection. The right coronary was large, the orifice somewhat reduced by an atheromatous plaque. The distal portion of the left anterior descending artery was anomalous, instead of extending to the apex it ended about two-thirds of the distance to the apex, just where the branch to the anterior horn arises. This branch was completely occluded with a partly organized clot. The infarct involved the superficial sinospiral muscle including the lower third of the anterior surface of the left ventricle, the lower anterior part of the septum, and the anterior papillary muscle. A small aneurysm was present at the very apex. The fibers of this muscle at the right apex were also softened. Findings confirming the experimental work are: great pain, slight fall of blood pressure, friction rub, a lesion definitely limited to the superficial sinospiral muscle, occlusion of a vessel known to supply this muscle, and the characteristic electrocardiogram, $R-T++++$. This infarct was probably not the sole cause of death, contributing factors being a general arteriosclerosis, abnormal cardiac rhythm and coma of 2 days' duration preceding death (cerebral accident).

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† The greater part of the clinical material was acquired while on service at Strong Memorial Hospital, Rochester, N. Y.

CASE 2.—Female, aged 29, with chronic syphilitic endocarditis and myocarditis. Died in Strong Memorial Hospital 5 days after an acute coronary accident. Electrocardiogram showed elevated *R-T* in all leads (Fig. 2). T_1 diphasic, T_2 and T_3 are positive. Scarring at the left apex and a recent anterior papillary infarct with a mural thrombus were found. Again the S.S.S. muscle is found injured when the only electrocardiographic sign is a tendency for the *R-T* to be +++ in the three leads, respectively.

CASE 3.—Female, aged 69, orthopnea and edema for years. Blood pressure on admission for decompensation 210/110. Heart much enlarged. Radial and retinal vessels sclerotic. Digitalized with improvement for 1 week. Twelve days after admission to Strong Memorial Hospital the heart sounds altered and gallop rhythm was marked. There was no pain and no friction rub. During the 5 succeeding days the blood pressure fell to 130/80 and on the fifth day after onset of the gallop rhythm the patient died. An electrocardiogram taken 3 days before death, 2 after the onset of the final decline, showed elevation of *R-T* in all leads (Fig. 3). The *T*-waves in all leads were positive. Autopsy and dissection revealed no pericardial involvement. The distal portion of the left anterior descending coronary was occluded. An organizing infarct of the apical intramural myocardium (2d portion of S.S.S.) and an organizing mural thrombus were found. Cardiac dilatation and hypertrophy, generalized arteriosclerosis, chronic mitral and aortic endocarditis and an infarct of the kidney were also present. In this case, there was *no pain*, neither was there any surface lesion. The blood pressure fell over a period of days but did not reach alarmingly low levels. It is felt that this infarct itself would not necessarily have been fatal in the absence of numerous contributing factors such as prior cardiac decompensation.

CASE 4.—Male, aged 70, ambulance admission to Strong Memorial Hospital, no history. Patient comatose, aphasic and cyanotic. An E.C.G. was obtained immediately on arrival, and was interpreted by one of us as an S.S.S. type and hence probably insufficient to explain the presenting signs (record almost identical with that of Case 2). A right hemiplegia was discovered. The patient was *in extremis* and died before morning.

At *autopsy* an embolism of the left middle cerebral artery and multiple small pulmonary infarcts were found. "The heart weighs 370 gm. A mural thrombus lies at the tip of the left ventricular apex. Cut section of this area shows marked thinning of the myocardium which is grayish red and laminated. This area extends but 1 cm. from the tip of the apex, anteriorly. Right ventricle not involved. No other localized myocardial lesions, only indefinite gray scarring. Right coronary artery slightly thickened. Left descending is markedly thickened with large areas of calcification but no definite occlusion. Here is an example of chronic infarction due to sclerosis, no complete occlusion, a definite lesion limited to the S.S.S. muscle, the characteristic slight elevation of *R-T* in all leads of the E.C.G. is present." Death was attributed to the cerebral accident.

CASE 5.—Male, aged 70, was admitted to Strong Memorial Hospital complaining of weakness, anorexia and 30 pounds loss of weight, these symptoms having appeared during the previous 6 months. Diagnoses of "uremia with glomerular nephritis, cancer of the stomach, secondary anemia, and arteriosclerotic heart disease were made."

The heart at *autopsy* showed: Weight 400 gm. Surface red and dotted with small sandy red particles. A few delicate fibrinous bands extended across the left ventricle. Fatty plaques on tricuspid leaflets and a 4 mm. area of ulceration midway on the leaflet surrounded by stone-like material. No changes in right chordæ tendineæ or papillary muscles. Right ventricle dilated, wall 5 mm. thick. Pulmonary valves normal. Mitral leaflets thickened and present fatty plaques. Left ventricular wall 1.7 mm. thick.

Coronary openings patent. Vessels tortuous and contain some fatty plaques and some calcification. Microscopic examination: "Epithelium thickened, edematous, infiltrated with fibroblasts, mesothelial cells, wandering cells and dark staining round cells. There are masses of dark pink staining granular homogeneous fibrin on the surface. The muscle fibers are slightly enlarged, fibrous tissue and fat lies between the muscle fibers. There is perivascular infiltration." This case is reported to indicate that thrombosis with infarction is not necessary to produce the S.S.S. type of electrocardiogram (Fig. 5; see discussion in Part I).

These 5 cases illustrate the outstanding clinical as well as the electrocardiographic signs of superficial sino-spiral lesions. It is seen that the electrocardiographic picture has no etiologic significance, *i. e.*, thrombosis, sclerosis, and pericarditis with muscle involvement each produce the characteristic picture, *R-T* slightly elevated in all leads. These lesions were all anterior; Case 3 involved only the internal (anterior papillary) portion of the muscle; Case 5 had pericarditis with muscle involvement; Cases 1 and 2 surface and anterior papillary infarctions; Case 4 infarction of the surface portion only.

Superficial Bulbo-spiral Muscle Lesions (hereafter called S.B.S.).

The E.C.G. and clinical picture characteristic of S.B.S. lesions are presented in 7 cases, of which 6 were verified by autopsy.

CASE 6.—Female (from the records of Dr. Jos. Sailer) was hospitalized for 3 months before death which followed repeated coronary attacks. The electrocardiogram showed marked depression of *R-T₁* and marked elevation of *R-T₃*. A prominent *Q₃* was present (Fig. 6). The heart was injected and Roentgen rayed before opening. An occlusion near the acute margin of the heart, in the right circumflex artery, was found. There was some involvement of the deep sino-spiral, but by far the greater infarction was in the superficial bulbo-spiral in its septal and posterior papillary regions.

CASE 7.—Male, aged 39, whose history dates back 12 years to a picnic when the patient ate and drank heavily and then played ball. There was collapse and a 45-minute period of unconsciousness without any convulsions and without any external injury. Thereafter he was confined to bed, had electrocardiograms, and was told that he had a "blood clot in the heart." For many years afterward he had pain on effort. He was always under observation at Strong Memorial Hospital thereafter, and was known to have rheumatic heart disease and myocardial insufficiency, Class I, 5 years before death, 7 after the picnic. During the last 7 years of life he had attacks of unconsciousness which were thought to be of circulatory origin. Aortic stenosis was diagnosed. Blood pressure usually about 170/80. He fell dead after running for a street car.

At autopsy the heart was found to be enlarged and a high degree of aortic stenosis was present. The heart muscle was normal except at the base of the inferior (posterior) papillary muscle where the inferior (posterior) wall was about half its thickness elsewhere. The inferior papillary muscle was paper-thin, it appeared to have scarcely any muscle fibers but consisted of a thin layer of scar tissue covered by endothelium. The coronary vessels were not diseased. In this instance, there is history of but one coronary attack which may have been an embolism. Certainly the lesion was limited to the superficial bulbo-spiral muscle. The electrocardiograms taken during the last 5 years of life, that is from the 7th to the 12th year after the attack, consistently show an *R-T* depression in Lead I and an elevation in Lead III

(Fig. 7). It seems doubtful that "injury current" could explain these $R-T_1$ displacements which lasted 12 years (Wilson³⁴ *et al.*).

CASE 8.—Female, aged 66, had diabetes and arteriosclerosis. Because of a gangrenous toe the left foot was amputated in Strong Memorial Hospital after which there was a cerebral accident and sudden death. Blood pressure 150/70. The electrocardiogram showed a depression of $R-T_1$ and elevation of $R-T_3$ which is characteristic of superficial bulbo-spiral lesions (Fig. 8). An old occlusion of the left anterior descending artery with a small aneurysm in the posterior apical portion of the superficial bulbo-spiral muscle was found.

CASE 9.—Male, aged 61, severe anginal attack 1 week before admission. Seven years ago had a "fainting" spell with dyspnea. Two years ago had effort pain. One year ago liver was said to be enlarged. Heart enlarged, loud harsh systolic murmur. Blood pressure 140/80. There was a dull ache in the lower abdomen for 4 days with *intense pain* one-half hour before death. Two electrocardiograms were of the superficial bulbo-spiral type (Fig. 9). The left anterior descending artery was occluded and old and recent *anterior* infarcts of this muscle found.

CASE 10.—Male, aged 51, was admitted to Strong Memorial Hospital for treatment of bronchopneumonia. He also had hypertensive arteriosclerotic heart disease. The electrocardiogram was of the superficial bulbo-spiral type, $R-T_1$ depressed, $R-T_3$ elevated (Fig. 10).

At *autopsy* an *anterior* infarction confirming the electrocardiographic diagnosis was found.

CASE 11.—Female, aged 61, progressive dyspnea for past year. Refused insurance 6 months ago (hypertension and angina). Heart enlarged, sounds poor quality, liver at umbilicus. Pulsus alternans, protodiastolic gallop at apex. Systolic pressure on admission to Strong Memorial Hospital 200 mm. Hg. The patient was restless and had sufficient pain to require opiates during a period of 19 days. Three days before death, fever appeared and the blood pressure fell to 150/95. Electrocardiograms taken on admission and again during the second week were of the superficial bulbo-spiral type (Fig. 11).

At *autopsy* general arteriosclerosis and severe coronary sclerosis were found. There was cardiac hypertrophy with dilatation. The left anterior descending artery had been occluded with old and new infarcts at the left apex posteriorly. A mural thrombus was attached to the left apex.

CASE 12.—Male, aged 45, had had 5 admissions to Strong Memorial Hospital in 2 years. Symptoms include pain, acute dyspnea, vomiting, orthopnea. The physical signs have been pallor, perspiration, edema, enlarged liver, soft apical systolic murmur, gallop rhythm. Blood pressure has ranged from 120/80 to 90/60. Four electrocardiograms taken over 2 years showed constantly the superficial bulbo-spiral characteristics (Fig. 12). Shortly after the fifth discharge the patient died at home during an attack. There was no autopsy. The case is included because of the typical history with a characteristic E.C.G. of an S.B.S. lesion, 5 known attacks preceding death.

Seven cases illustrating superficial bulbo-spiral lesions are presented, 6 of these were proven at autopsy. The clinical signs are the same as for S.S.S. lesions, *i. e.*, much pain and moderate fall of blood pressure appearing over a period of several days. Cases 8 and 11 are instances of *posterior* lesions following occlusion of the left anterior descending artery, Case 7 is a posterior papillary lesion, artery involved undetermined, Cases 9 and 10 were left anterior descending occlusions with only anterior involvement of the muscle,

Case 6 was posterior involvement from occlusions of the right coronary. Again we emphasize that the characteristic electrocardiogram appears not in association with involvement of some one artery, not always in relation to the anterior or the posterior surface but constantly in the presence of a lesion of the one muscle band.

Deep Sino-spiral Lesions.

CASE 13.—Male, aged 60. (Patient of Dr. E. C. Reifenstein, Hospital of the Good Shepherd.) The chief complaint was of substernal pain, radiating down both arms, of $2\frac{1}{2}$ hours' duration, associated with collapse. He had been bothered with "hyperacidity" but had no history of severe cardiac pain until the second day before admission, when it was brought on by exertion, walking after meals, and was relieved by rest. On the day of admission the pain came on early in the morning without previous exertion. It was not relieved by nitroglycerine. Two hours after the onset he was writhing with pain, covered with perspiration, face pale, the pulse full, bounding, regular, 48 to the minute. Blood pressure, 140/80. The pain gradually lessened after morphine. Twelve hours later there was still pain. The heart rate was 126, regular, and the heart sounds, which in the morning had been good, were now feeble. Moist râles were heard at the bases. The condition was thought to be very serious. The electrocardiogram taken on the first day of the severe attack shows elevation of the $R-T_1$ and great depression of $R-T_3$ (Fig. 13). All standard leads show positive T waves. The record is typical of a D.S.S. lesion. The following day the blood pressure was 90/80. For the succeeding 5 days there was slight improvement, the systolic blood pressure reached 100. Ten days after the attack the blood pressure was 108/80. The heart sounds were of better quality, no cyanosis was present and the oxygen tent was discontinued. There had been no friction rub. From the end of the second to the twelfth day pain was not a prominent feature. On the following day he complained of "heart burn." The pulse rate was 60, regular, the sounds of poor quality, the blood pressure again 90/66. There had been fever constantly from the second day on. The morning of the fourteenth day he was comfortable with no signs of congestive failure, could lie prone without dyspnea, no râles, heart not enlarged. Toward evening there were periods of irregular heart action associated with a smothered sensation, extreme apprehension, and fear of death. During these attacks he was pale, hands were blue, pupils were dilated, pulse very irregular in force, rate and rhythm. An hour later the heart suddenly failed, respiration ceased after the heart had stopped.

Autopsy (Dr. Ferguson): "The heart weighs approximately 400 gm. The left coronary artery shows marked yellowish thickening and calcification with some areas of narrowing of the lumen and other areas of apparent dilatation. Just within the orifice of the left coronary artery there is a small amount of reddish brown thrombic material which is rather loosely attached to the underlying endothelium. *Extending from the bifurcation of the left coronary there is a mass of grayish brown thrombic material which appears to occlude the entire lumen of the descending branch for a distance of about 3 cm.* The artery in this area shows marked calcification. The myocardium of the entire *anterior* wall of the left ventricle and of the anterior two-thirds of the interventricular septum appears markedly softened and somewhat thinned out. The endocardium of the left ventricle over the anterior portion of the interventricular septum, and the anterior wall of the left ventricle extending from just below the aortic valve to the apex, appears reddish and yellowish in color, apparently due to changes in the

underlying myocardium. Scattered over the surface, but particularly near the apex are numerous irregular masses of reddish brown thrombic material. There is a flattened mass of yellowish brown thrombic material on the endocardium of the right ventricle over the interventricular septum. On section the myocardium in the before mentioned areas shows considerable thinning with numerous irregular yellowish brown areas of necrosis and apparent hemorrhage. The borders of the areas of necrosis appear somewhat edematous. The right coronary artery shows a few scattered areas of yellowish thickening with slight calcification. The valves are without evident lesion." The 3 cm. long thrombus blocked the branch to the left portion of the deep sino-spiral muscle. Since the whole anterior descending artery was also blocked the ischemia must have involved the deep sino-spiral and the superficial sino- and bulbo-spirals. The great extent of the lesion, particularly the septal involvement makes it equally certain that the predominating terminal lesion was in the deep sino-spiral.

CASE 14.—Female, aged 73, complained of precordial stabbing pain on effort for 12 days before admission to Strong Memorial Hospital. There had been dyspnea for 2 years, edema for 1 year, and orthopnea for 2 weeks. Turning in bed or walking brought on the pain. The electrocardiogram 13 days after onset (Fig. 14) was typical of a D.S.S. lesion. Two days after admission (1 day after the E.C.G.) another acute attack occurred. The blood pressure fell rapidly from 190/100 to 60/40. The following day still another acute seizure took place and this was followed by death. No autopsy was available. The case is mentioned to illustrate pain on effort, with profound drop in blood pressure in the presence of this type of electrocardiogram.

CASE 15.—Female, aged 45, had been under care repeatedly for rheumatic endocarditis and was admitted to Syracuse Memorial Hospital with a decompensation which did not respond to treatment. She was orthopneic and much distressed by the pain of phlebitis which involved her left leg and right arm. Temperature was considerably elevated. Cardiac pain was *not prominent*. The decompensation increased and death resulted. The electrocardiogram taken 2 days before death was similar to several taken during the hospitalization (Fig. 15). Complete heart block was present. If one spaces the *P* waves and then considers cycles where the *P* does not fall on the down stroke of *R* the criteria of a deep sino-spiral lesion (*R-T+—*) are seen to be present.

The unopened heart was injected with bismuth-gelatine solution and Roentgen rayed. An occlusion was found in the posterior portion of the right circumflex artery. Dissection confirmed a lesion of the posterior septal portion of the deep sino-spiral, the adjoining posterior wall, and to a much less extent the posterior papillary muscle (this has a multiple blood supply). There was a chronic mitral endocarditis (stenosis and regurgitation) with a large anterior papillary pushing up to make a small funnel-shaped opening. Both the aortic and tricuspid valves were the seat of active endocarditis with many friable vegetations. The infarcted area was non-hemorrhagic, pale and mushy. The occlusion may have been embolic. There was no coronary sclerosis.

CASE 16.—Male, aged 58, was admitted for treatment of decompensation. Six weeks after digitalization, while still in the Strong Memorial hospital, he developed an arrhythmic tachycardia and suddenly died. Electrocardiograms taken on the day of admission and again 2 weeks before death showed a progressive deep sino-spiral lesion (Fig. 16).

At *autopsy* the heart weighed 790 gm. On cutting the left apex a large anterior infarcted area measuring 10 by 8 cm. was noted. The overlying epicardium was covered by a heavy white scar. The myocardium in this area was completely replaced by scar tissue. There was an overlying mural

thrombus 4 cm. thick. The coronaries were tortuous and calcified. The distal third of the left anterior descending was occluded. In this heart the branch to the left portion of the deep sino-spiral came off the left anterior descending, unusually low (distal). The size of the infarct ensures involvement of the deep sino-spiral muscle.

CASE 17.—Male, aged 44, died in Strong Memorial Hospital of papillary squamous cell carcinoma of the left kidney, with metastases. The electrocardiogram showed low voltage in all leads with $R-T$ elevation in I, $R-T$ depression in III (Fig. 17): Metastatic nodules were found in the anterior surface of the right ventricle, penetrating into the deep sino-spiral layer. The S.S.S. is also involved but the deep sino-spiral picture predominates.

CASE 18.—Male, aged 72, history of *effort pain*. Admitted to Strong Memorial Hospital 4 days after a coronary attack, in shock. Blood pressure, 90/50. There were tarry stools. There was no recovery from the shock; death occurred 8 days after the onset. The E.C.G. 6 days after the onset of coronary pain showed the typical D.S.S. picture (Fig. 18). The QRS in no lead exceeded 0.10 second. Heart block was present, P is on the upstroke of R_1 and quite separate from the R cycles shown in II and III.

At *autopsy*: General arteriosclerosis with marked coronary sclerosis. Mitral endocarditis with stenosis was present. There was occlusion in the proximal portion of the left anterior descending, above the branch to the deep sino-spiral. There was also a duodenal ulcer.

CASE 19.—Male, aged 16, had been a "blue baby." The cyanosis persisted, always cold and dyspneic on exertion. The dyspnea and cyanosis increased during his sixteenth year. Fingers and toes were clubbed. Retinal fundi dark red. Heart enlarged in all diameters. A harsh, low pitched, blowing, systolic, pulmonary murmur was heard. R. B. C. 8,100,000; W. B. C. 6200. The electrocardiogram showed a "right axis deviation," but since Leads I and III do not equal II, the degree is uncalculable (Robb and Robb, 1931²³). The $R-T$ in Lead I is much elevated, while that in Lead III is frankly depressed (Fig. 19). Such changes indicate a lesion in the deep sino-spiral muscle.

At *autopsy* a patent foramen ovale and a pulmonary stenosis were found. There was no coronary disease, the right ventricle was hypertrophied and dilated.

As previously explained, the right ventricle is mainly composed of the deep sino-spiral muscle. Also the increased mechanical load in pulmonary stenosis comes on the right ventricle. Comparable examples of D.S.S. electrocardiograms in the presence of congenital lesions involving the right ventricle are to be found in reports by Abbott,^{1a} "Pulmonary stenosis with ventricular septal defect" (Fig. 68, p. 290); also Congenital Pulmonary Stenosis, the case of Alexander, Knight and White³ (Fig. 77, p. 304). Abbott^{1b} in her atlas provides an additional instance in Plate XXIII (Fig. 3 c) "complete (crossed) transposition, aorta and pulmonary artery from reversed ventricles. Ventricular septum entire, and ductus arteriosus closed. Foramen ovale patent. Dilatation of aorta and *great hypertrophy of Right Ventricle*." This case confirms not only the electrocardiographic localization, but also supports the opinion that "coronary" waves are not specific for any one type of disease. Ten years ago one of us showed reversible coronary waves following pH changes of the perfusate in the turtle heart.²⁷

Deep sino-spiral lesions are demonstrated in 7 cases, 6 of which

were proven at autopsy. The localization of the muscle involvement was as follows: Nos. 13, 16, 18 were infarcts resulting from occlusion of the left anterior descending coronary and were anterior lesions; No. 17 was a right anterior involvement, No. 21 involvement of the whole right ventricular portion of the D.S.S.; No. 15 was a posterior lesion resulting from occlusion of the right coronary. Again left and right anterior, posterior, and septal lesions are described, all having two findings in common: that the D.S.S. muscle is damaged and that the electrocardiograms show elevation of $R-T_1$ (or $S-T_1$) and depression of $S-T_3$.

Deep Bulbo-spiral Lesions, as already mentioned, are difficult to obtain clinically. The records of the electrocardiographic service of Strong Memorial Hospital were placed at our disposal through the great kindness of Dr. Wm. McCann. Among approximately 1000 records of deceased patients only 3 of this type were to be found. Two of the 3 came to autopsy. We do not think that any one of these 3 electrocardiograms is typical of a *pure* deep bulbo-spiral lesion. Experimentally, small branches can be ligated which supply this muscle alone. Clinically, involvement of this muscle would result most frequently from occlusion of the left circumflex, the very origin of the left anterior descending, or the main trunk of the left coronary artery. If these larger vessels are occluded other muscles will suffer as well. At the best, then, one can only hope to find electrocardiograms approaching the type of those characteristic of the experimental lesion together with a history and physical findings similar to the experimental picture (Figs. 1-2-3, Part I).

CASE 20.—Male, aged 45, chief complaint of attacks of unconsciousness. Studies made after his admission to Strong Memorial Hospital led to a diagnosis of brain tumor for which he was operated on December 14, 1936. The tumor was found to be of vascular origin with an arteriovenous communication and was inoperable. Following the operation, he did not do well. On December 16, 1936, at 8 A.M. he had an attack diagnosed as coronary thrombosis (Fig. 20). The blood pressure dropped at once from a systolic of 190 to 110/60. The pulse became totally irregular, the blood pressure fell continuously, death occurred at 1.10 P.M. In the notes there was no specific mention of pain.

At *autopsy* the coronary arteries were found to be tortuous and thickened. The most proximal portion of the left anterior descending was found to be narrowed and was also occluded with a friable clot 8 mm. in length. There was marked thinning at the apex. "At the right lateral margin of the left ventricular wall about *one-third of the distance from the base of the heart* there is a fairly definite line of demarcation in the color of the myocardium. On the left lateral wall this color change begins about *one-third of the distance up from the apex and extends* from this point upward and laterally to join the right margin as described above. Below this area the myocardium is dull mottled and grayish yellow, above it is very deep red and meaty." Microscopic examination showed fragmentation in hypertrophied fibers, no nuclei in the area of deep redness, many neutrophils, fibrin on the epicardial surface. At the right ventricular apex section showed necrotic muscle and neutrophils. The localization to the basal third of the heart

together with a definite occlusion at the very origin of the vessel ensures a deep bulbo-spiral involvement.

CASE 21.—Female, aged 76, was admitted to Strong Memorial Hospital on July 14, 1936, complaining of headache, vertigo, nausea, vomiting and some abdominal pain. She had always been unusually strong and well. Her present illness began during a period of great heat and she gave the impression that she had heat prostration. There were râles at both bases; blood pressure was 120/90, W. B. C. 17,300; temperature 39°, heart rate 150. The lips were cyanosed and there was slight edema of the ankles. The peripheral vessels were sclerosed, the heart was enlarged and fibrillating. During 2 days she received 1.4 gm. of digitalis. On July 16, 1936, she complained of *substernal pressure*, the blood pressure fell to 98/70, the lungs were "wet" with dullness at the right base. Straw colored fluid (175 cc.) was removed. On July 18, 1936, an electrocardiogram showed an "auricular rate of 280, ventricular rate 130, left axis deviation, and myocardial damage." Some portions of a long record showed flutter and other portions fibrillation. The patient died suddenly on this day. Figure 21 was taken shortly before death. The recorded diagnosis was: "Arteriosclerotic heart disease with decompensation, heat stroke, questionable coronary occlusion."

Autopsy: "The heart weighed 480 gm. The epicardium at the tip of the right ventricle and over the left ventricle was red and granular. The left anterior descending artery was markedly calcified and contained a thrombus at its origin. There was considerable atheroma and calcification throughout the coronary system. The right ventricular apex was dull yellow and above this was stippling of fatty degeneration. The left ventricular apex was filled with adherent clot, 4 cm. in diameter. The left ventricular wall toward the septal side showed dull yellowish completely dead muscle. *Half the septum* was necrotic. Toward the base the muscle was firmer and reddish brown. The necrotic portion was ballooned out, the wall 0.5 cm. thick. The papillary muscles were large; one showed areas of necrosis. Microscopic examination showed fibrin on the surface with dilated capillaries beneath, edema and fibrin in the subepicardial fat, intimal sclerosis of the arteries. In the muscle extensive necrosis with vacuolated, poorly staining fibers. Again the fact that the origin of the left anterior descending artery was occluded, the extent of the infarct, especially the great septal involvement, makes damage to both superficial muscles, the deep sino-spiral and the deep bulbo-spiral certain. In the electrocardiogram the deep bulbo-spiral characteristics predominated. (Note also the presence of Q_s .)

CASE 22.—Female, aged 54, for 25 years had been known to have rheumatic heart disease, mitral stenosis and aortic insufficiency with many periods of decompensation. She was admitted to Strong Memorial Hospital on August 5, 1935, complaining of a persistent severe pain beneath the left scapula which had appeared that morning. Blood pressure, 140/80. She appeared acutely ill, was orthopneic, had no cough, was cyanosed. There were râles over the lungs. The heart was markedly enlarged with a heaving precordial pulsation, the point of maximum impulse in the 6th I. S. anterior axillary line. Action was irregular, sounds of poor quality. A loud blowing systolic and a softer diastolic murmur were heard at the apex, and a short rough systolic at the pulmonary area. Impression of the admitting officer was "chronic rheumatic endocarditis with failure, auricular fibrillation, pulmonary embolism." On August 10, 1935, an electrocardiogram showed "left axis deviation, auricular fibrillation and myocardial damage." On August 20, 1935, abdominal paracentesis yielded 2700 cc. of clear fluid. On August 25, 1935, she complained of a "pain between the shoulders," was nauseated and vomited. The heart rate dropped to 27.

She gradually improved, the heart rate rose rapidly from 50 to 120, râles appeared all over both lungs, cyanosis was marked, dyspnea extreme, blood pressure fell rapidly and death promptly ensued (Fig. 22).

These 3 histories illustrate deep bulbo-spiral involvement. One man of 45 died without pain 5 hours after his first coronary attack, 1 woman died on the same day as her first complaint of substernal pressure, and the third, a woman, died of an acute seizure during decompensation of rheumatic endocarditis and subsequent to pulmonary and axillary embolism. In each of these instances the electrocardiogram has a form characteristic of a deep bulbo-spiral lesion. All three show lowered voltage, and relatively very high takeoff of $R-T$ in all leads, with most of the T waves positive. For a more complete review of lack of, or variations in, type of pain reference should be made to Kennedy's recent study in 200 autopsied cases.¹⁶

Mixed Lesions. Whether this method is of value either for empirical localization or as an aid to prognosis when disease is widespread must be considered. Seven cases (23 to 29 incl.) with histories, electrocardiograms and autopsies were obtained which did not show characteristics for any one muscle lesion. At autopsy, all 7 proved to have 2, 3, or 4 muscles involved. To conserve space the protocols of 2 only (Cases 23, 26) are offered. The electrocardiograms of Cases 27 and 28 are reproduced so that the compound forms may be recognized.

CASE 23.—Male, aged 68 (patient of Dr. W. E. Barnett), had been hypertensive for 20 years and had had a coronary attack 10 years ago. On June 13, 1937, there was increased anginal pain. The blood pressure was 220/160. The electrocardiogram (Fig. 23 A) shows the down stroke of R_1 thickened, $S-T_1$ slightly depressed, $S-T_3$ but slightly elevated. Such a combination indicates more than one lesion. Another attack of thrombosis occurred on June 16, 1937, after which the blood pressure fell to 110/70. Record 23 B taken 2 days later shows a further depression of $S-T_1$ and elevation of $S-T_3$. Death came on June 21, 1937. The uncut heart was sent for examination; it was large, unusually blunt and also discolored at the apex. The right ventricle was unduly small, the right auricular appendage undeveloped, the left appendage infarcted. The coronary vessels were unusually large, tortuous, calcareous, and the left anterior descending occluded below the branch to the deep sino-spiral. The blunt apical region, about one-third of the whole heart, was covered by a subendocardial hemorrhage 1 cm. thick. A large aneurysm occupied the whole apical region. On section, it was difficult to distinguish the muscular wall, both superficial muscles were replaced by scar tissue. The hemorrhage was contained in the sheath of these muscles.

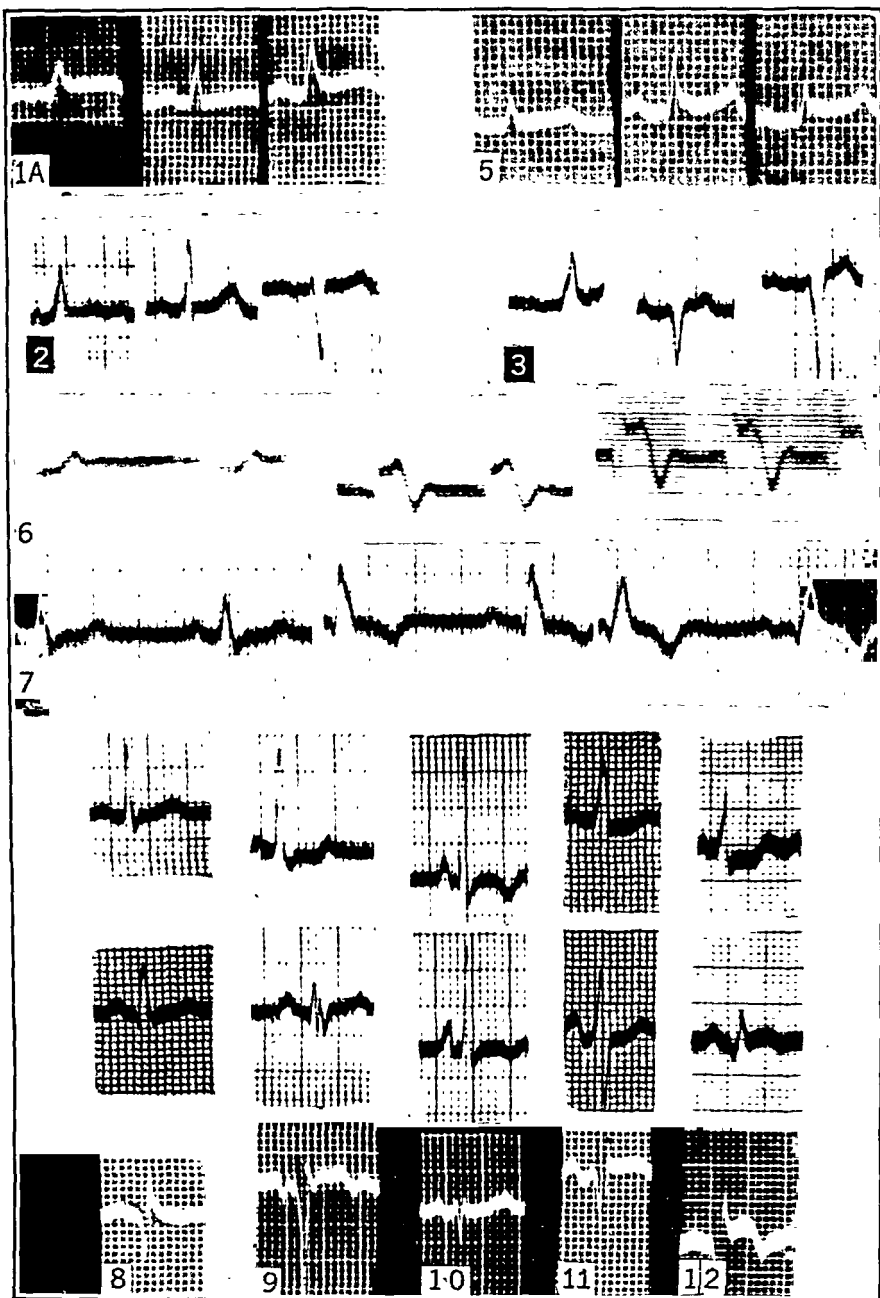
This extensive involvement of both superficial muscles in an individual having a blood pressure of 220/160 supports the experimental observation that these muscles are not responsible for the maintenance of the circulation. Anterior and posterior walls were about equally involved which may have made T_1-T_3 localization less satisfactory.

CASE 26.—Male, aged 63 (history reported through courtesy of Dr. W. D. Paul from the service of Dr. Fred Smith, University Hospitals, Iowa City), had had thyroid treatment for myxedema for 5 years and had repeatedly stopped the medication because of substernal pain. Shoveling coal induced an attack followed by 4 hours of unconsciousness, after which he was admitted to the hospital (December, 1934). Upon admission the blood pressure was 125/70 though it had previously been up to 170/100. There was marked retinal sclerosis. He improved and remained in the hospital as an ambulatory patient, again taking 5 grains of thyroid extract (B. W.). On January 15, 1935, at 7 A.M., a severe attack of pain necessitating morphine occurred, and after 5 hours another excruciating attack was experienced. Electrocardiograms were taken at 8 A.M. and at about 2.30 P.M. and again a few minutes before death $\frac{1}{2}$ -hour later (Fig. 26). Records taken in 1929 show $S-T_1$ depression and $S-T_2$ elevation, an S.B.S. lesion which could have been caused by the narrowing of the distal portion of the left anterior descending artery. This type of record persisted but in the tracing taken an hour before death the voltage has decreased a little and the $S-T_1$ depression is less as is also the $S-T_2$ elevation. The clinical history of another severe attack of pain plus this change is interpreted as indicating involvement of the more basal muscles. The D.S.S. (+ — —) added to the S.S.S. and S.B.S. would explain the change. Finally, a few minutes before death, the $R-T$ takeoff begins at the very peak of R which is characteristic of D.B.S. lesions. The heart weighed 520 gm. There was an area 1 cm. in diameter on the anterior surface with a recent fibrous adhesion. At the apex and posteriorly were numerous depressed gray areas. On cut section, the apex, the greater part of the posterior wall, part of the septum and part of the anterior wall all show scarring. In some places the muscle is almost replaced by scar tissue. The lumen of the coronary vessels is reduced, there is a fresh occlusion of the right posterior descending and the left anterior descending is so sclerosed as to be almost obliterated. The last finding accounts for the persistent S.S.S. and S.B.S. involvement and the recent occlusion for the involvement of the D.S.S. and terminally of the D.B.S. Using the muscle bundle method of analysis the progress of coronary disease can be visualized and related to the progressive anatomic changes. Anterior *vs.* posterior localization could scarcely have been so satisfactory since both anterior and posterior lesions were present.

Analysis of such cases justifies the inference that in the presence of signs and symptoms of coronary disease, if the electrocardiogram does not conform to one of the four types described for localization, more than one muscle bundle has been injured.* When a progressive change from one characteristic type to another is found, especially with lowered voltage appearing, the prognosis is more serious because more muscles are being damaged.

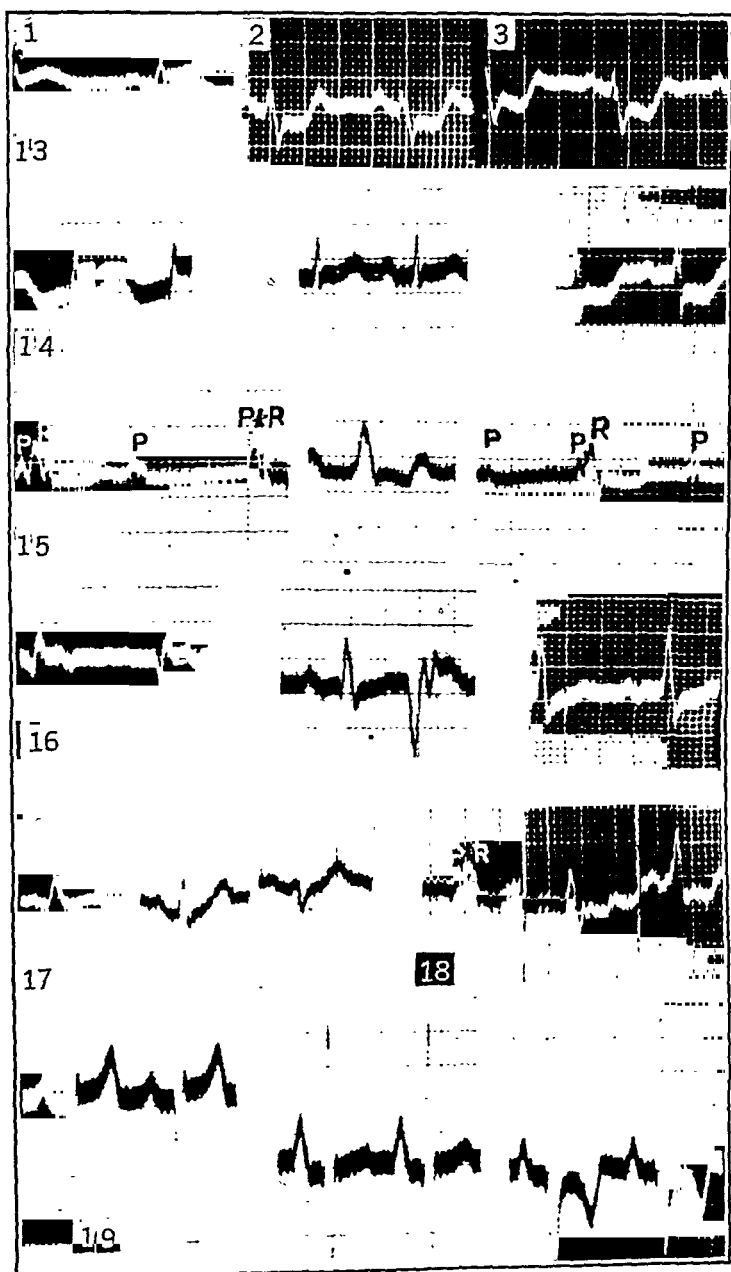
Summary and Conclusions (Parts I and II). 1. The T_1 , T_2 method of localization is valuable where infarcts occur in the more common localities and under these conditions there is close agreement with the muscle bundle method.

* None of the electrocardiograms reproduced by Wood, Wolferth and Bellet³⁶ as examples of left lateral localization are typical of single muscle lesions and would have been interpreted by us as "mixed" lesions. (No infarcts of this region with the possible exception of Case 23 were present in our whole series, which reflects its relative rarity.) Our Figure 1 (Part I) shows that the left circumflex artery supplies four muscles in the left lateral region of the ventricle, hence its occlusion would inevitably produce a mixed lesion. Furthermore, Vessel No. 17 of the left-circumflex is distributed (together with No. 8) to the S. A. node. This fact is the anatomical basis for their conclusion that left lateral infarction and auricular fibrillation are often associated.

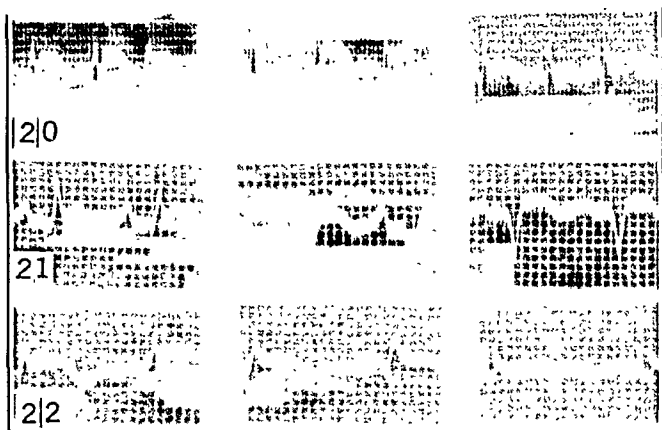


FIGS. 1, 2, 3, 5.—Electrocardiograms for cases of similar numbers. Note moderate elevation of $R-T$ in all leads. In each instance the lesion was limited to the S.S.S. muscle, E.C.G. for Case 4 omitted, since essentially like Case 2. Three standard leads arranged horizontally.

FIGS. 6 to 12.—For cases with same numbers. Each shows $R-T_1$ depressed and $R-T_3$ elevated, in each a lesion in the S.B.S. muscle was found. Three standard leads were arranged horizontally for Cases 6 and 7, vertically for all others. Figs. 8 and 11 were associated with posterior lesions from occlusion of the left anterior descending artery; Fig. 6, was present with a posterior lesion following occlusion of the right circumflex artery; Figs. 9 and 10 are from anterior lesions with occlusion of the branch of the left anterior descending to the S.B.S.; Fig. 7, taken 12 years after an embolism which involved the inferior papillary portion of the S.B.S. only. There was no coronary disease but a marked aortic stenosis. Five similar E.C.G.'s taken respectively in 1930, 1931, 1933, May, 1935, and October, 1935, following the single coronary attack in 1923 are on file. The $R-T$ displacements are present after 12 years.



FIGS. 13 TO 19.—All show elevation of $R-T_1$ and depression of $R-T_3$. Each proved to have a lesion in the D.S.S. muscle. In Cases 13, 16, 18 the occlusion was in the proximal portion of the left anterior descending and the lesion was anterior. In Case 15 the right circumflex was occluded near the posterior sulcus, the blood supply to the bundle of His was interrupted, block resulted. There was a large posterior infarct. Case 19 shows the same $R-T$ displacements where the muscle injury was due to overwork and overdistention in the presence of congenital pulmonary stenosis. There was no coronary disease. Case 17 had a cancer nodule in the right anterior portion of this muscle.



FIGS. 20 to 22.—The characteristic to be noted in these D.B.S. lesions is the relatively very high takeoff of the *R-T* in all leads. There is commonly lowered voltage and a tendency for the *T* waves to be positive in these badly damaged hearts.

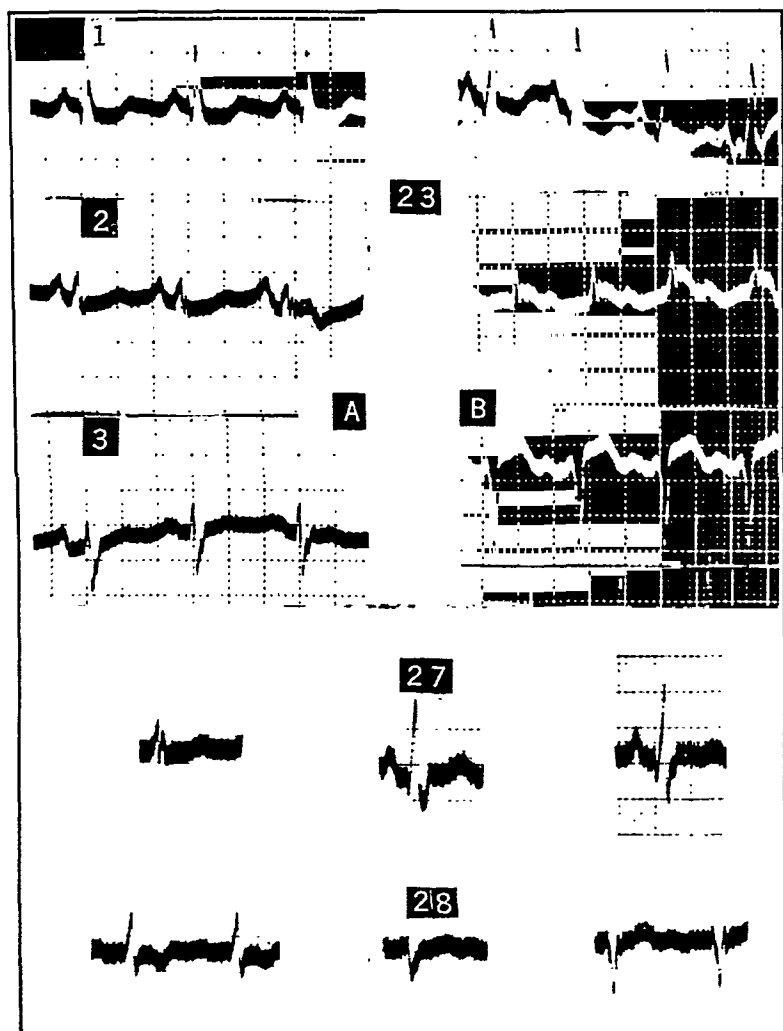


FIG. 23.—E.C.G. taken 10 years after one coronary attack and 2 days after another. Fig. 23 *b* taken 2 days after *a*. An S.B.S. lesion is surely present and probably an S.S.S. too because the *S-T₁* is more nearly iso-electric than one would expect with the degree of *R-T₁* elevation present. Both were found to be replaced by scar tissue at the apex where an aneurysm large enough to hold a golf ball was found. Anterior and posterior walls were about equally damaged. Electrocardiograms of Cases 24, 25, 29 are not reproduced since they are fairly similar to those of Cases 27 and 28.

FIGS. 27, 28.—It is seen that these records do not conform to any one of the four characteristic types. Multiple muscle lesions were found in each.

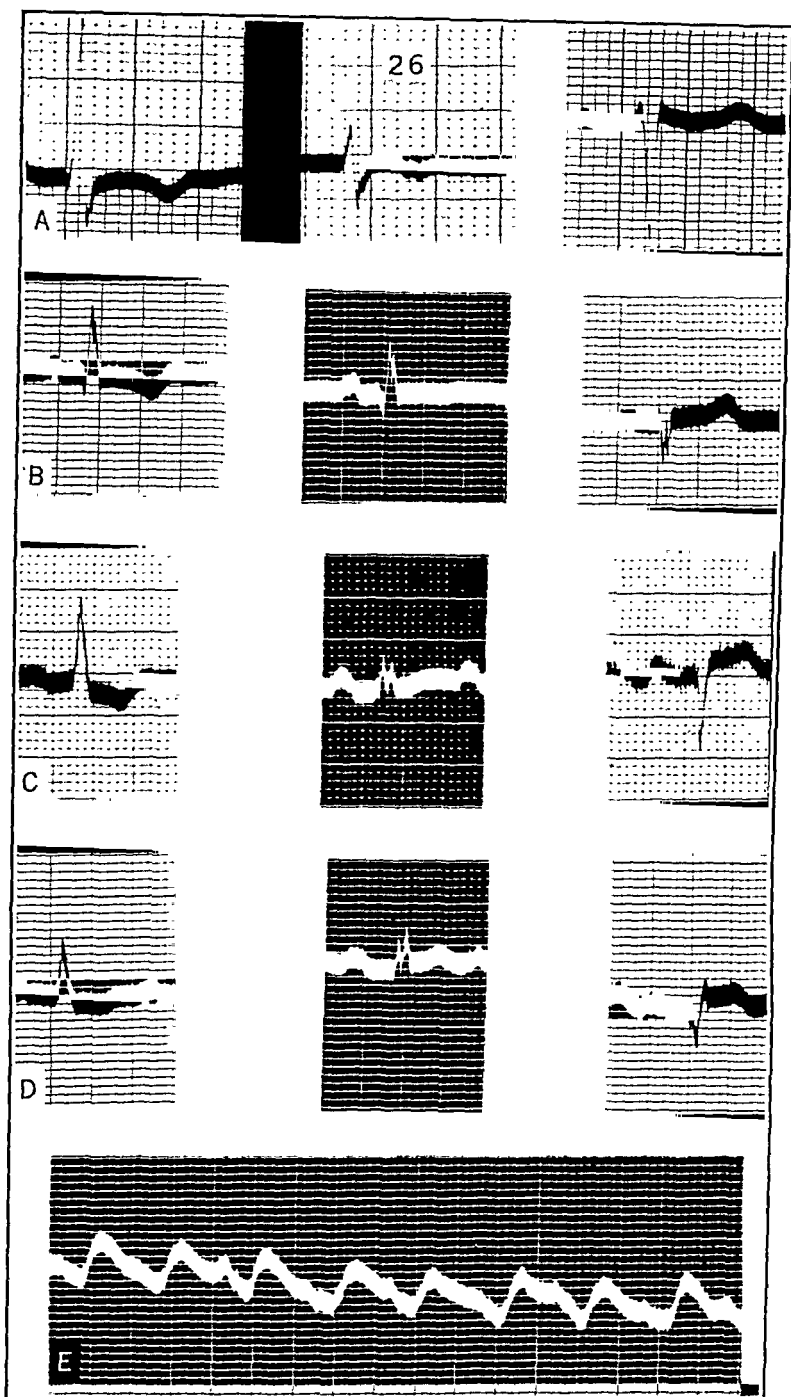


FIG. 26.—Five records of Case 26, *A* taken in 1929, *B* in December, 1934, *C*, January 15, 1937, at 8 A.M., *D* the same day at 2.30 P.M., and *E* a few minutes before death at 3.00 P.M. Note the progressive change in the *R* contours and in voltage. An older S.S.S. and S.B.S. lesion is complicated by a D.S.S. and just before death by a D.B.S.

2. Numerous authors report difficulty in localization when the infarcts involve an unusual site. When a reciprocal relation of T_1 to T_3 is lacking, application of this principle becomes difficult. It is shown that this reciprocal relation often is lacking.

3. The muscle bundle method of localization, supported by experimental work, has been applied to the analysis of 77 cases, 48 with adequate autopsy reports from literature and 29 new reports. When one of the four characteristic electrocardiograms appears there is no doubt as to the muscle involved but to specify which portion, or the extent of the lesion, or the cause of the disturbance in conduction within the one muscle bundle is not possible.

4. A short review of the superficial and deep bulbo- and sino-spiral muscles together with their function and blood supply is offered.

5. As a "thumb nail" diagnostic method one may ignore Lead II and note that $R-T_1$ depression indicates involvement of the S.B.S. muscle; if $R-T_3$ is depressed the D.S.S. must be implicated; an S.S.S. lesion raises both $R-T_1$ and T_3 above the iso-electric level. $R-T$ takeoff from the peak of R (or near the peak) in all leads, especially in the presence of low voltage, indicates a D.B.S. lesion. Inequality of the R bases is to be sought and its presence is more instructive than its amplitude.

6. Clinical findings may fortify the experimental conclusions and the E.C.G. interpretation in the following respects: Severe pain is often present when the superficial muscles are involved and if the lesion is anterior a friction rub may be heard. Deep muscle injuries precipitate large and abrupt falls of blood pressure associated with variegated and atypical pain sensations generally accentuated by effort.

7. Inference as to etiology from the E.C.G. alone is not justified since many different pathologic changes may result in a similar effect on conduction.

8. Displacements of $R-T$ do not disappear as rapidly clinically as when infarction is experimentally produced by ligating a vessel in an otherwise normal heart, for seldom does one find in man occlusion of one vessel without disturbance of the collateral circulation (See Gross and Calef¹²).

9. We confirm the findings of Harris and Hussey¹³ and of Gross and Calef¹² modifying the conclusion of the latter to read "occlusion of the left anterior descending coronary artery *proximal to the branch to the D.S.S. and distal to the origin of the circumflex branch* results in $R-T_1$ elevation and $R-T_3$ depression." It is shown that this type of record can be obtained from right and from posterior lesions as well.

10. The superficial muscles may be infarcted repeatedly and death may ensue when a deep muscle is eventually involved, or from some non-cardiac cause.

11. The prognosis for D.S.S. lesions is graver and treatment of an attack should be more rigid and much more prolonged.

12. Infarcts of the D.B.S. are even more serious and often result in sudden death.

These data could not have been reported without coöperation. Our sincerest thanks are extended to all who have aided, in particular to Dr. W. S. McCann, Professor of Medicine, University of Rochester, who placed his records at our disposal, and to Dr. S. W. Clausen who also granted us that courtesy. Dean George H. Whipple of Rochester, University School of Medicine and Dr. Wm. B. Hawkins have been most generous in allowing us to have uncut hearts. Dr. E. C. Reifstein, Professor of Medicine at Syracuse University College of Medicine, Dr. Charles Post, Dr. J. G. F. Hiss, and Dr. Irving Ershler also coöperated in providing histories and material. Dr. J. Howard Ferguson, Dr. Tyree Wyatt, Dr. James Wilson, and Dr. Arthur Harris are warmly thanked for providing hearts for examination. Dr. W. E. Barnett of Logansport, Indiana, Dr. Marguerite McCarthy, of Syracuse, and Dr. W. D. Paul from the service of Dr. Fred Smith of Iowa City have each provided 1 valuable case with complete data. Finally, one history, electrocardiogram and autopsy verification were obtained from the records of the late Dr. Joseph Sailer of Philadelphia. We regret that to conserve space it has been necessary to omit much of the clinical data (especially protocols for Cases 24, 25, 27, 28, 29) and in Cases 4, 24, 25, and 29, the electrocardiograms as well. These data will be supplied upon personal request.

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THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA BY HYDROXYETHYLAPOCUPREINE.

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OUR first clinical report¹⁻⁴ on the results of the treatment of pneumococcic pneumonia from 1935 to 1937 by hydroxyethylapocupreine was made last year. The present paper is a further analysis of the data from a similar group of cases occurring during the past year, from July 1, 1937, to June 30, 1938.

In the analysis of our mortality figures there are three facts to which we desire to refer very briefly. We are aware of their triteness. The death rate for pneumonia per 100,000 population shows that Pittsburgh has consistently a very much higher mortality than any other large city in the country. For the past 3 years it has been 161, 193 and 167, respectively. Comparative figures for most of the large cities can be noted in the City of New York Department of Health, Quarterly Bulletin. We hold no brief for the accuracy of these figures from different cities, but one would imagine that errors would be probably about the same for each city. The Pittsburgh death rate, according to this data, is frequently twice that of many of the other cities. Our material, therefore, comes from a community in which pneumonia is a severe disease. The type of human beings who make up the majority of the cases studied in any pneumonia series must be considered as having an influence on the mortality rates. In the public ward service of any large city hospital a fair percentage of the pneumonia patients present evidence of alcoholism, malnutrition and physical neglect. It is logical to expect that the mortality in pneumonia of this group will be decidedly higher than in private cases in their homes or in hospital private rooms. Our cases in the first 2 years were over 90% from the public ward and last year the figure was 81%. It is important, therefore, to keep the human element in mind when comparing statistics regarding pneumonia. Since the last week in December, 1936, we have been impressed with the frequency of postinfluenzal

pneumonia which in our cases has been a mixed infection. *Strep. hæmolyticus* and *H. influenzae*, considered as the most frequent secondary invaders following virus infection, have been present in cultures from the sputum in from about one-half to two-thirds of our cases over this period of time, whereas in the 2 previous years these organisms were not commonly found. We believe it is almost as important from a bacteriologic point of view to culture the sputum as it is to differentiate the pneumococcus into its different types. The mixed infections undoubtedly present a changed clinical picture from pure pneumococcic pneumonia, and at autopsy they are definitely different. It is by no means always an easy matter to be certain of the influence of the *Strep. hæmolyticus* and *H. influenzae* in any given case of pneumonia, particularly early in its course, when one finds in culture of the sputum these organisms associated with the pneumococcus. Atypical clinical courses are suggestive of more than pure pneumococcus infection. A subsequent *Strep. hæmolyticus* empyema would logically point to the influence of this organism on the pneumonia while delayed resolution and the *Strep. hæmolyticus* similarly appear to be closely related. It is our opinion from clinical observations only, that in mixed infections the results with the chemical have not been as good as when the case appeared to be a relatively pure pneumococcic infection.

Hydroxyethylapocupreine dihydrochloride was given in capsules by mouth, 15 gr. every 3 hours day and night for 3 to 5 days. In some patients, it produced nausea and occasionally vomiting. However, in only a few cases was it necessary to discontinue the chemical for this reason. It may be that in the future the base or another salt will be used by mouth instead of the dihydrochloride. For intravenous use, a monohydrochloride solution is given, each 50 cc. containing 15 gr. and this is injected into the vein every 3 hours. The monohydrochloride solution is readily made by dissolving 15 gr. (1 gm.) of the hydroxyethylapocupreine dihydrochloride in 50 cc. of distilled water (a 2% solution) and to this solution adding slowly about 2.5 cc. of normal sodium hydrate. The solution becomes milky at first but clears when the monohydrochloride stage is reached. The intravenous solution is given slowly, from 7 to 10 minutes being taken for the 50 cc. At this rate, there have been no reactions. If given rapidly, a weak rapid pulse may be noted with some fall in blood pressure. We have seen very few reactions of this kind and we feel fairly certain that their cause is carelessness due to speed in the injection of the chemical. In 3 years we have seen no evidence of visual disturbance. Thrombosis of the veins of the arm at the point of injection with the intravenous method does occur at times especially if the veins are difficult to enter, but it is less with the monochloride than with the dihydrochloride.

As in the previous 2 years, no one under the age of 15 has been

included in our analysis of treated cases. Drs. M. L. Menten and R. MacDonald will later report their results on the treatment of children from the Children's Hospital, Pittsburgh. Postoperative pulmonary conditions also have been excluded so as to avoid confusing collapse and embolism with pneumonia.

During the past year in our 149 chemically treated patients we have had 2 cases of pneumococcic empyema. Both were surgically drained, although 1 had had the hydroxyethylapocupreine injected into the pleural cavity according to the method we described in our previous paper. These cases recovered.

Two pneumococcic empyema cases that had not been chemically treated for the pneumonia, but were admitted after the empyema had developed, showed in 1 at autopsy endocarditis and empyema. The other patient was a man of 75 in whom surgical drainage was required after several injections of the chemical into the pleural cavity. He recovered. There were 3 empyemas in children, ages 6 to 9 years. Two received chemical treatment for the pneumonia while 1 had Type I serum. The last case made a prompt recovery from the empyema with intrapleural injections of the hydroxyethylapocupreine. One of the first 2 recovered with surgical drainage, but the other died from massive collapse of lung following the surgical interference. This last case had previously been given the chemical injections into the pleural sac.

There were 3 cases of *Strep. hæmolyticus* and 2 of *Staph. aureus* empyema. One of the latter followed a severe trauma but the remainder were the end results of what we considered postinfluenzal pneumonia with mixed infection. The empyemas were treated surgically, 2 recovered and 3 died; 1 death followed a severe hemorrhage from the lung almost 2 months after an apparently good recovery. The exact cause of this hemorrhage was not determined.

The small percentage of Type I pneumonia has been typical of the Pittsburgh infection in all hospitals for many years. Type II pneumonia has shown a steady increase during the past 3 years as the percentage figures 13, 16 and 32, respectively, would indicate. During the past year, this type of infection was not only the most frequent, but also showed the highest mortality. The undetermined types were cases outside of our hospital where typing had been negative with I, II, V, VII and VIII serum, but not carried further. There were 5 cases on the table showing multiple types, and in a comparatively large number, noted as unclassified, we could not establish the type of pneumococcus.

The bacteremia chart shows the important part played by Type II pneumonia in our cases of last year. This type comprised 62% of all the bacteremia cases and 59% of our Type II pneumonias had a bacteremia. In our experience, the finding of Type II pneumococcus in blood cultures rarely ever is associated with a mild infection even with low or absent colonies on the poured plates. The undetermined cases are the same as those referred to in the first table.

The data on the serum cases was kindly furnished by Dr. Philip Marks, of the Department of Public Health, Pittsburgh, and includes all serum-treated cases from our hospital. The city of Pittsburgh supplied, free and

TABLE 1.—THE RESULTS OF TYPING IN 204 CASES OF PNEUMONIA.
1937-1938.

Type.	No. of cases.	Percentage.
I	26	12.7
II	66	32.3
III	23	11.6
IV	3	1.47
V	8	3.9
VI	1	0.49
VII	8	3.9
VIII	10	4.9
IX	3	1.47
X	2	0.98
XI	1	0.49
XII	4	1.95
XIII	3	1.47
XV	1	0.49
XVI	3	1.47
XVII	1	0.49
XVIII	2	0.98
XX	2	0.98
XXII	2	0.98
XXIII	1	0.49
XXV	2	0.98
XXVIII	3	1.47
XXIX	1	0.49
XXXII	2	0.98
IV, VII, XXIX	1	0.49
V, XVI, XVIII, XXIX	1	0.49
XIII, XXI, XXVIII	1	0.49
II, XVIII	1	0.49
III, IV	1	0.49
Unclassified	14	6.85
Undetermined	7	3.43

TABLE 2.—ANALYSIS OF BACTEREMIA CASES. 1937-1938.

(176 cases had daily blood cultures taken during the febrile period of the disease; of these, 62 were positive, 35.2%.)






Type.	No. of bacteremia cases.	Percentage.
I	4	6.45
II	39	62.9
III	8	12.9
V	3	4.84
VII	1	1.61
VIII	1	1.61
XII	1	1.61
XX	1	1.61
XXV	2	3.22
XXXII	1	1.61
Undetermined	1	1.61

Incidence of Bacteremia According to Type.

Type.	No. of cases.	Bacteremia cases.	Percentage.
I	26	4	15.4
II	66	39	59.1
III	23	8	34.7
V	8	3	37.6
VII	8	1	12.5
VIII	10	1	10.0
XII	4	1	25.0
XX	2	1	50.0
XXV	2	2	100.0
XXXII	2	1	50.0
Undetermined	7	1	14.2

liberally, specific serum for Types I, II, V, VII, VIII and XIV to all cases where the disease was not beyond the end of the third day. The first two items in Table 3 have included all cases in the treated and non-treated groups even if the patient died a few minutes after admission to the hospital in the non-treated group, or in the treated group if only a single dose of the chemical was given. We feel that the "two days in hospital" figures give a more accurate estimation on which to draw conclusions, although the results in the two groups relatively are almost the same. The "no specific treatment" cases, with few exceptions, entered the hospital after the fourth day of the disease.

TABLE 3.—ANALYSIS OF PNEUMONIA CASES.

	No. of cases.	1937-1938.	Percentage died.
No specific treatment	41		56.2
Hydroxyethylapocupreine (any)	167		25.7
No specific treatment (in hosp. 2+ days)	30		40.0
Hydroxyethylapocupreine (2+ days)	149		17.4
Specific serum	285		22.0

There were 24 additional chemically treated cases on whom blood cultures were not made; nearly all of these cases were at home, but a few were in other hospitals. Blood culture data on the serum-treated cases of the city of Pittsburgh series were unfortunately not available for comparison with our material in Table 4.

TABLE 4.





	No of cases.	1937-1938. Bacteremic Cases	Percentage died.
No specific treatment	8		87.5
Hydroxyethylapocupreine	36		61.1
Non-bacteremic Cases			
No specific treatment	21		23.8
Hydroxyethylapocupreine	89		3.3

Table 5 indicates that with one exception all of the recovered bacteremic cases were of the first three types and as Type II represented 62% of our bacteremias, it is logical that most of the recoveries were of this infection. All of the non-bacteremic Type II cases (15) recovered.









To Table 7 of our previous paper for the years 1936-37 should be added 4 more cases with bacteremia which recovered. These cases occurred in the months of May and June; the table as published was for 10 months only. The types were I, II, VII and an undetermined higher type. The highest

colony count was 44 in Type II, 1 in Type VII and pneumococci in the broth only in the other two types. In the past 3 years there have been 37 cases with bacteremia which have recovered, and in 8 of this number, the colony count has been 33 or more. We have not seen a recovery in a non-specifically treated case (serum or chemical) with a bacteremia above 15 colonies per c.mm. of blood over a period of 8 years when blood cultures have been taken daily or very frequently during the febrile course of the pneumonia. We are aware that others have described such cases and we do not doubt their occurrence, but they must be very infrequent.

TABLE 5.—RECOVERED CASES WITH BACTEREMIA. 1937-1938.

Sex.	Age.	Type.	No. of positive cultures.	Highest colony count.
M.	39	I	2	0
M.	20	II	2	0
M.	47	II	2	3
M.	41	II	2	1
M.	54	II	4	96
M.	45	II	1	4
M.	39	II	3	33
M.	32	II	2	0
F.	58	II	1	0
M.	40 (?)	II	1	0
M.	41	II	1	0
M.	59	III	4	187
F.	35	III	2	0
M.	55	XXV	2	0





TABLE 6.—COMPARISON OF SERUM AND CHEMICALLY TREATED CASES.

	No. of cases.	Type I.	1937-1938.	Percentage died.
Serum	90			13.3
Hydroxyethylapocupreine	16			12.5
Type II.				
Serum	124			32.2
Hydroxyethylapocupreine	39			35.9
No specific treatment . . .	12			58.3
Type III.				
Hydroxyethylapocupreine	18			22.4
Types IV,V,VII,VIII.				
Serum	70			15.7
Hydroxyethylapocupreine	24			16.6

In comparing the results of serum-treated cases in Pittsburgh as reported by the Department of Health with our chemically treated cases of the same types during the same period of time one sees very little difference.

The combining of serum and chemical, particularly in Type II, will probably be tried next year if the infection retains the virulence it appeared to possess during the past year. This could also apply to the other types for which there is an available specific serum. Experimentally, there is considerable evidence in the past to show that optochin increased the protective power of specific serum and we have noted the same with hydroxyethylapocupreine. The reader is referred to White's⁵ excellent book on *The Biology of Pneumococcus* for the discussion of this phase of the problem.

TABLE 7.—COMPARISON OF HOME AND HOSPITAL CASES TREATED WITH SERUM AND CHEMICAL.

	No. of cases.	1937-1938.	Percentage died.
Specific serum (home)	126		13
Specific serum (hospital)	159		29
Hydroxyethylapocupreine (home)	27		8
Hydroxyethylapocupreine (hospital)	122		19

This chart shows, both for serum and chemical, the difference between hospital and home mortality. Our hospital cases treated with chemical were almost all public ward patients, and in our opinion their poorer human fiber accounts to a great extent for the difference in mortality.







TABLE 8.—ANALYSIS OF FATAL CHEMICALLY TREATED CASES. 1937-1938.

Age.	Sex.	Type.	Bacteremia.	No. pos. cultures.	High count.	Remarks.
46	M.	I	Pos.	3	0	Autopsy, diffuse active caseous bronchopneumonia, left upper lobe; lower left lobe Type I pneumonia.
35	F.	I	Neg.	Acute encephalitis.
33	M.	II	Pos.	3	*	
37	M.	II	Pos.	1	15	
37	M.	II	Pos.	5	600	Autopsy, postinfluenzal pneumonia.
39	M.	II	Pos.	3	94	Delirium tremens.
54	M.	II	Pos.	5	*	Delirium tremens.
43	M.	II	Pos.	1	0	Delirium tremens.
22	M.	II	Pos.	12	26	Endocarditis, pneumococcic.
35	M.	II	Pos.	3	11	Delirium tremens.
34	M.	II	Pos.	5	3	
19	M.	II	Pos.	5	3189	
29	M.	II	Pos.	1	0	Autopsy, acute encephalitis, postinfluenzal pneumonia.
28	M.	II	Pos.	1	1	
29	F.	II	Pos.	2	0	
39	M.	II	Pos.	5	4500	
48	M.	III	Pos.	2	9	Autopsy, acute coronary thrombosis.
45	F.	III	Neg.	Acute coronary thrombosis—clinical evidence only.
74	M.	III	Pos.	1	0	
70 (?)	M.	III	Not taken			
41	M.	V	Pos.	3	3800	
31	M.	V	Pos.	5	98	
21	M.	VII	Neg.	General peritonitis, probable ruptured appendix.
72	F.	VII	Pos.	3	7	
35	M.	XXXII	Pos.	4	1	Acute encephalitis.
38	F.	(undetermined)	Pos.	2	0	

* Innumerable.

Dr. Permar demonstrated during the past year fairly frequently at the autopsy table postinfluenzal pneumonia which is always a mixed infection. There were a number of examples of this infection among the "no specific treatment" cases which are naturally not in the above list. Only those cases coming to autopsy have been considered as postinfluenzal pneumonia in the above analysis, although from the clinical and bacteriologic examination of the sputum there were several more of this type. Pneumococcus was present in all. Acute encephalitis in 2 instances was the diagnosis by clinical and spinal fluid examination. In the third case, autopsy confirmed the clinical diagnosis. It was seen several times in the "no specific treatment" group. We did not have a case of pneumococcus meningitis during the year. In the peritonitis case, the febrile course of the pneumonia had dropped to normal by lysis. This was followed rapidly in the course of 24 hours by typical signs of general peritonitis. Appendiceal origin was considered most likely by the surgical department and by us. Operation, on account of the state of the patient, was considered inadvisable and an autopsy was not obtainable. Several other autopsies were done in this group but the findings were typical of pneumococcic pneumonia and are, therefore, not noteworthy.

TABLE 9.—SUMMARY, 3 YEARS, 1935-1938.

	No. of cases.	All Cases	Percent. age died.
No specific treatment	136		50.0
Hydroxyethyl-apocupreine	329		24.9
Bacteremic Cases			
No specific treatment	41		82.9
Hydroxyethyl-apocupreine	97		61.9
Non-bacteremic Cases			
No specific treatment	90		32.2
Hydroxyethyl-apocupreine	193		9.3

The "no specific treatment" cases as in the other tables were, with few exceptions, ill at least 4 days on admission. In some of the hydroxyethylapocupreine cases this year treatment began on the fourth day and a few even later.

It will be noted in Table 10 that the number of cases on the third day of disease when chemical treatment began was much larger than on any of the other days. We purposely withheld the chemical until the third day in many instances. In our hospital work we do not see very many admissions on the first day of disease. Cases appearing within 10 to 12 hours after onset were treated, otherwise the chemical was withheld until 2½ days after the onset. In our first clinical report we noted the low mortality in cases when treatment began on the third day and it was

to test this observation further that we withheld treatment. Table 10 still shows the lower mortality of the third day cases, but we believe much larger numbers should be analyzed to prove the observation prior to attempting to explain the fact. There have been a few cases this year which have not been included among the treated group where chemical has been given within a few minutes to 2 to 4 hours after the initial chill. These patients were not in the hospital so that Roentgen rays were not taken. They were all adults and 2 or 3 had bloody sputum in which pneumococci were found. The temperature promptly came down inside of 24 hours and remained normal. No typical physical signs ever developed so they were not included as pneumonia cases. We noted a few cases of this type last year. They are likely only seen in private practice, but undoubtedly in the future this group may form a very interesting class to watch. The ideal time to use the chemical may be immediately following the chill. This would apply, therefore, almost entirely to the practitioner of medicine rather than to the hospital physician.

TABLE 10.—MORTALITY ACCORDING TO DAY OF DISEASE WHEN FIRST TREATED.

	No. of cases.	1935-1938.	Percentage died.
First day	67		28.4
Second day	53		35.9
Third day	128		17.9
Fourth day :	50		38.0
Fifth + day	25		27.9

Conclusions. 1. The mortality figure in pneumococcic pneumonia in adults during the past year has been greatly reduced in those cases which received hydroxyethylapocupreine.

2. In comparing the mortality figures of our chemically treated cases, which were, of course, smaller in number, with the serum-treated cases in Pittsburgh for the same types of pneumonia, during the same period of time, almost identical results were observed.

3. Hydroxyethylapocupreine has shown no evidence of disturbing vision.

The authors wish to express their thanks to Dr. H. H. Permar for his help during the past year.

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THE BLOOD PLATELET COUNT IN RELATION TO THE MENSTRUAL CYCLE IN NORMAL WOMEN.

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CASES of thrombocytopenic purpura occurring periodically with menstruation have been recorded, especially by Minot.¹⁶ In these individuals the blood platelets decreased rapidly to very low numbers near the onset of menstruation and returned to normal values during the intermenstrual period. In chronic thrombocytopenic purpura a further decrease of the platelets may occur at the time of menstruation accompanied by an exacerbation of symptoms. Denisova-Suscevska⁸ observed such a case for 22 years. These observations suggest that an abnormal exaggeration of a physiologic cyclic process associated with menstruation may be responsible for the decrease of platelets.

The present investigations were carried out in an effort to determine if there was any regular variation in the number of blood platelets during the menstrual cycle in normal women and to evaluate the conflicting reports on this subject. The problem has received little study and the investigators who have reported a regular variation are not agreed on the type or amount of change, nor during which part of the menstrual cycle it occurs.

Pfeffer and Hoff¹⁸ were the first to report a distinct decrease in the number of blood platelets with the onset of menstruation. Henning,¹¹ Francesco,⁹ Sakai,¹⁹ Benhamon and Nouchy,⁴ and Kato¹³ have confirmed these observations. Brinck and Patrunky⁵ demonstrated a decrease in platelets during the premenstrual period in normal subjects. Dameshek⁷ recorded a fairly constant intermenstrual figure, varying with the individual subject, but with the appearance of the menses he always observed a sudden and marked rise in the blood platelet count. Hirsch and Hartmann,¹² Denisova-Suscevska,⁸ and Morse¹⁷ were unable to demonstrate any cyclic change in the number of blood platelets in normal women.

While the present investigations were in progress, Genell¹⁰ reported observations on the variations in the number of blood platelets during the menstrual cycle. The data are much larger and more convincing than any previously recorded, although only average values for a group of 38 women are given. Genell concluded that the platelets varied in a regular manner which was characterized by the occurrence of the lowest values on the first and second menstrual days, a subsequent rise which reached a peak after several days, and later a premenstrual decrease.

Methods. Tocantins^{21a} has recently presented an excellent review of the technical methods for the enumeration of blood platelets and states that in experienced hands direct methods give greater accuracy than indirect ones. When each step is standardized and the manipulative procedure coördinated most of the objections raised against the use of the direct method are overcome. In the present study, the number of blood platelets were determined by direct counts on capillary blood with the aid of an isotonic diluting fluid containing a stain and anticoagulant. The stain is not essential.

The diluting fluid used was with slight changes Edwards' modification of Buckman⁶ and Hallisey's fluid. Its composition was 8 gm. of cane sugar, 2 gm. of sodium citrate and 0.04 gm. of brilliant cresyl blue made up to 100 cc. with distilled water. All glassware used was scrupulously clean. The sodium citrate and sugar were dissolved in a portion of the distilled water, filtered and placed in a volumetric flask. The stain was ground in a mortar and transferred into the flask by washing. This solution was shaken thoroughly and allowed to stand 6 hours with frequent agitation. It was then made up to volume with distilled water. The solution was centrifuged at 2000 revolutions per minute for 30 minutes and pipetted into a clean glass-stoppered bottle. It was stored in an ice-box with a temperature of from 5° to 10° C. This solution can be kept in this manner for many months and under these conditions is bacteriostatic. Blank counts from time to time were never over 5000 platelet-like bodies per c.mm. A small amount of solution was filtered each day as needed. The unused portion was never returned to the stock bottle.

Freely flowing capillary blood was obtained from a deep stab wound in the ear lobe with a sharp No. 8 Keith's abdominal surgical needle fixed in a cork. If blood for other purposes was obtained from the same puncture the sample for platelet determination was always taken first. The blood was drawn to the 0.5 mark in a certified red blood cell counting pipet and diluted immediately to the 101 mark with the platelet diluting fluid. The pipet was sealed with a rubber band and shaken immediately in an automatic shaker for 5 minutes. A counting chamber with improved Neubauer ruling certified by the United States Bureau of Standards was then filled. The preparation was allowed to stand in a moist chamber for 15 minutes before counting the platelets. The number of platelets per c.mm. was calculated by counting those present in 2 sq. mm. and multiplying by 1000. A high dry objective with magnification of $\times 400$ was used. The simplest areas in which to count the platelets are the squares to the right and left of the finely ruled center area. The distribution was checked each time by comparing the values for each of the sq. mm. spaces. The fine adjustment of the microscope was used continually to obtain the necessary critical focusing. Only characteristic highly refractile forms of round, oval or comma shape (if seen in profile), varying in size from 1 to 5 micra, were counted. Irregularly shaped débris, bacteria, fat globules and other minute objects could be readily eliminated by the experienced eye.

Experimental. The average of all platelet counts done on normal women in this laboratory by the author in the past 2 years, using the above method, was 265,000 per c.mm. The normal range in women is extremely wide as will be shown later. The average for normal males was approximately 300,000 platelets per c.mm., with a range of from 250,000 to 400,000.

The present investigation required repeated observations on the number of blood platelets making it necessary for the counts to be made on capillary blood. However, a preliminary study was made

on 8 women to compare the numbers of platelets in venous and capillary blood. When venous and capillary blood was taken simultaneously, 126 determinations showed that the values for venous blood were persistently higher than those for capillary blood. The platelet counts on venous blood averaged 15% more than those on capillary blood. This difference has also been reported by Tocantins.^{21b} However, the difference was consistent and therefore direct platelet counts on capillary blood obtained from the ear were satisfactory for a statistical study.

A total of 1034 blood platelet counts were made on 13 normal white women. The subjects were unmarried laboratory technicians, ranging in age from 19 to 40 years. All had a normal menstrual cycle from 25 to 31 days in length and normal menses of 4 to 5 days' duration. There was no serious illness in the group during the period of observations and none showed purpuric manifestations or presented abnormal bleeding. The number of blood platelets were observed during a total of 82 menstrual cycles. No subject was followed for less than 3 complete cycles. No definite seasonal variation in the blood platelet level was noted, although this study was begun in October, 1936, and terminated 1 year later.

The subjects had very little dysmenorrhea. Seven individuals took no drugs whatsoever and 6 occasionally took 5 to 15 grains of aspirin in the first or second day of the period. It should be emphasized that no drugs were taken before the onset of the menstrual flow.

All platelet counts were done at about the same time of day (10 A.M.). The effects of food and exercise which might influence the counts were fairly constant at this hour. During the early part of the investigation platelet counts were occasionally performed on the same subject twice daily. However, it was soon found that there was rarely any significant difference between the morning and afternoon values. In compiling the data if there was more than one determination on any particular day the average was taken. Throughout the 82 menstrual cycles there was an average of one determination every other day.

Seventy-five per cent of the blood platelet counts were done by the author and the remainder by an experienced technician. It was found that the results obtained by one individual checked with those obtained by the other within a range of 20,000 platelets per c.mm. Based on the average of 265,000 platelets per c.mm., this admits a technical error of approximately from +4% to -4%.

The 1034 blood platelet counts on 13 normal women, during a total of 82 menstrual cycles are recorded in Figure 1. Each dot represents a platelet count which is plotted in relation to the day of onset of the menses thus enabling the data on various subjects to be superimposed. Mean values were calculated for each day of the cycle and a line drawn connecting these points on the chart.

The mean values and the median values are almost identical. The average daily blood platelet count shows a variation in relation to the menstrual cycle. The average platelet count is at its lowest level on the day of onset of the menses (220,000 per c.mm.). Following this there is a rapid rise to about 275,000 per c.mm. The number remains rather constant at this level until 2 weeks before the onset of the next period. During the 2 weeks premenstrual period there is a slow progressive decrease in the number of blood platelets.*

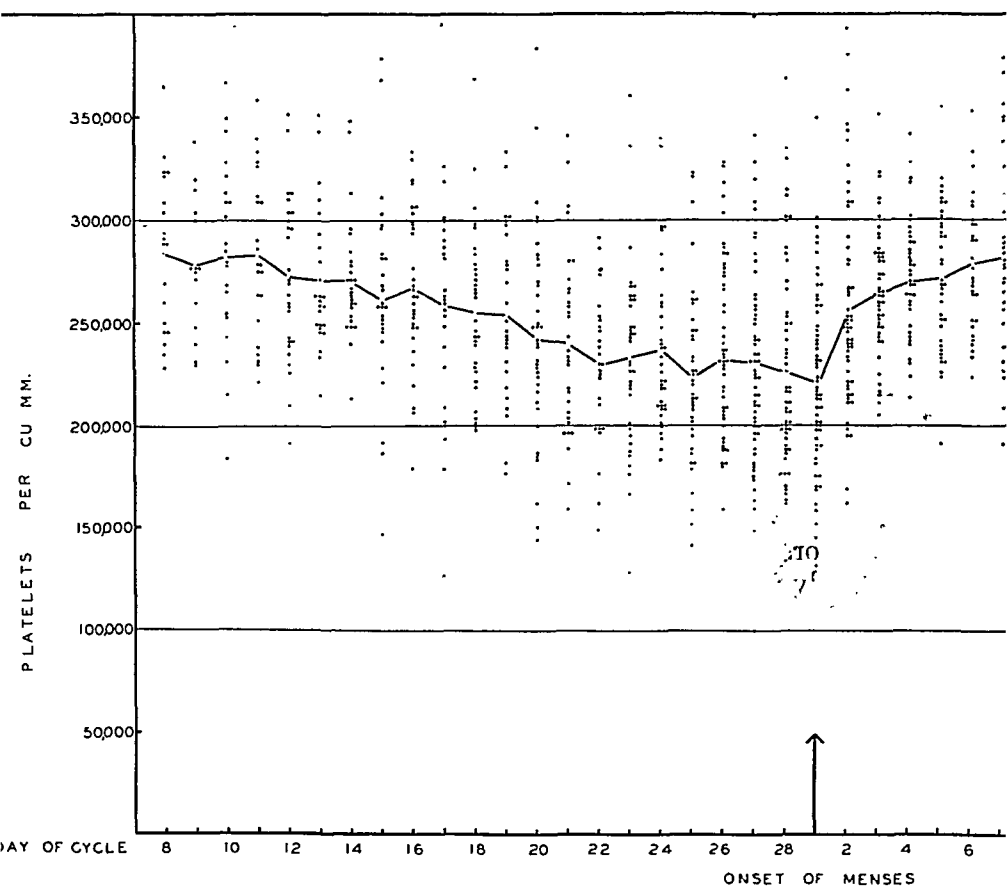


FIG. 1.—Blood platelet counts during 82 menstrual cycles in 13 normal women plotted in relation to a "28-day" menstrual cycle. (..... average.)

The average number of blood platelets in relation to the menstrual cycle in these cases and in Genell's¹⁰ cases are shown in Figure 2. Genell used Kristenson's¹⁴ method for the enumeration of the platelets which is similar to the method used in the present study. These two groups show approximately the same variation

* A regression line was fitted to this slope and proved to be significant by the (t) test.

in the number of blood platelets in relation to the menstrual cycle. The major discrepancies lie in the lower figures obtained by Genell on the first and second days of menstruation and the more prolonged postmenstrual rise..

An analysis of the platelet counts for each of the 13 women studied or for each of the 82 menstrual cycles studied showed significant variations from the average data for the entire group. Variations greater than the range of technical error ($\pm 4\%$), took place only during the *premenstrual phase*. It has been assumed, for analytical purposes, that a minimum variation of 60,000 platelets

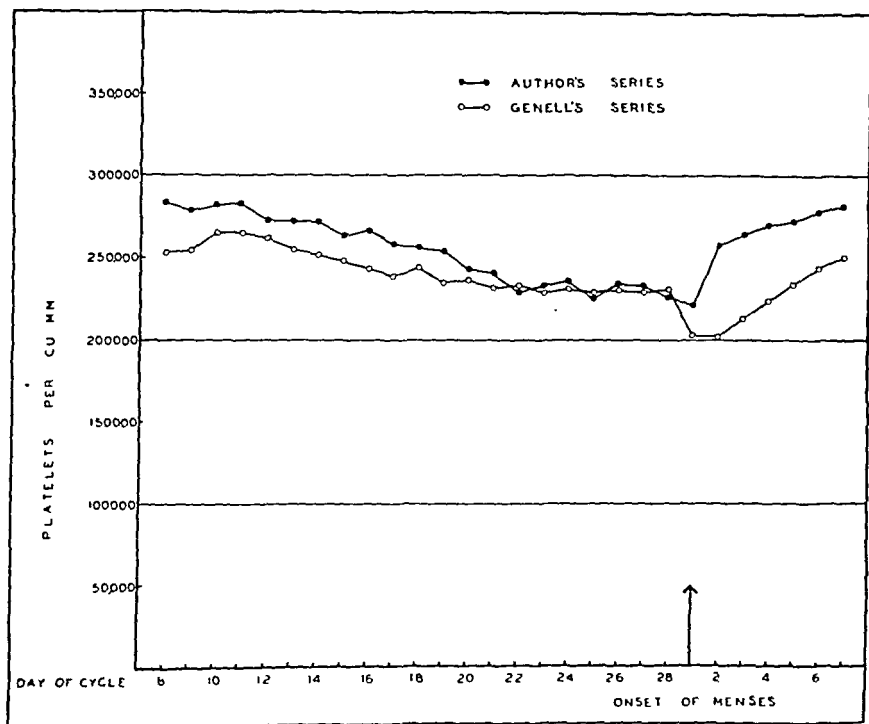


FIG. 2.—Comparison of the daily average number of blood platelets during the menstrual cycle observed by Genell and by the author.

per c.mm. of blood ($\pm 12\%$), checked on more than 1 day, was a significant fluctuation. On this basis the results in the total 82 menstrual cycles studied may be summarized as follows: 57 of the cycles showed a premenstrual decrease in the number of blood platelets, 22 showed no premenstrual change and 3 showed a premenstrual increase. All instances of a premenstrual rise in the number of platelets occurred in 1 individual. Seven subjects repeatedly showed a premenstrual decrease in the number of blood platelets and 5 only occasionally. In 1 subject a premenstrual decrease was suggested with alternate menstrual cycles. Figure 3 shows the rhythmical fluctuations in the blood platelet count during four consecutive menstrual cycles in 1 subject. The data in this

figure are typical of that obtained for all the individuals consistently showing a premenstrual decrease of the platelets. Other cases occasionally showed a more rapid and marked premenstrual decrease in the platelets (*e. g.*, from 350,000 to 150,000 per c.mm.) but such changes were exceptions rather than the rule.

Disregarding the 3 instances of a premenstrual increase in the blood platelets, which occurred only occasionally in 1 individual, and assuming that a decrease and no change are equally likely, the expected number of cycles showing a premenstrual decrease is 39.5. The observed number was 57 and the deviation from the mean is therefore 17.5. The probability of a chance deviation as great as the one observed is approximately 1 in 10,000.

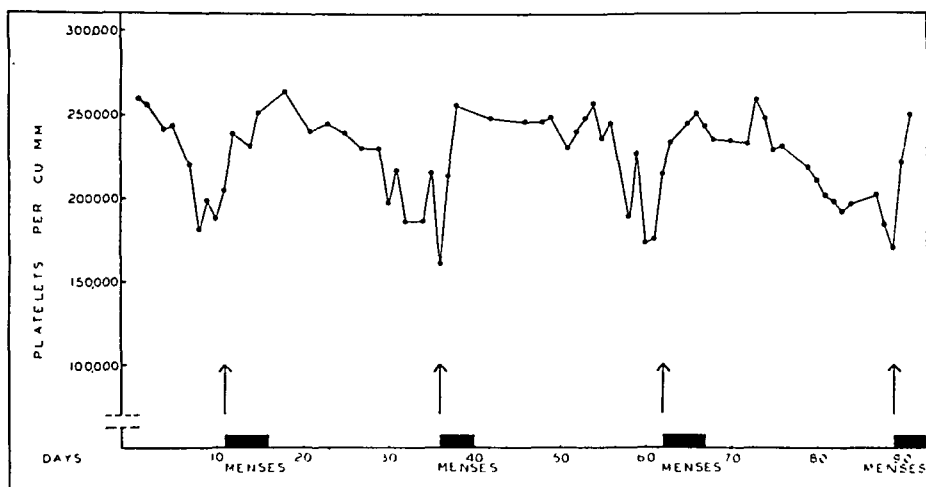


FIG. 3.—Variations in the blood platelet count during four consecutive menstrual cycles in a normal woman.

White blood cell counts and differential white blood cell counts were made simultaneously with blood platelet determinations on these subjects on 122 occasions. The white blood cell count and differential count failed to show any regular variation in relation to the menstrual cycle. The reticulocytes were not abnormally few at the time when the platelet counts were at the lowest levels. The bleeding time (Duke's method) occasionally seemed to be slightly increased during the premenstrual period. However, the method is entirely inadequate for measuring slight changes.

Discussion. The lack of agreement among earlier investigators in regard to a regular variation in the number of blood platelets in relation to the menstrual cycle in normal women may be explained by the limited observations and the fact that all individuals do not respond in an identical manner. This is substantiated by the fact that Genell's¹⁰ and the present studies give more data than previous reports and the results obtained were entirely similar.

The mechanism producing the usual regular variation in the blood platelet count in relation to the menstrual cycle is unexplained.

Genell believed that the postmenstrual rise was an increase above the normal platelet level due to absorption of necrosed endometrium.

It has long been known that hemorrhage usually causes an increase of blood platelets. The amount of blood loss necessary to cause a rise in the platelet count is not known. It probably varies tremendously in different individuals. Recent studies (Levertson and Roberts,¹⁵ Widdowson and McCance,²² and Barer, Fowler and Baldridge³) have shown the average amount of blood lost with each menstrual period is a little less than 50 cc. We removed 15 cc. of blood daily for 5 days from a normal male and from a normal female during the intermenstrual period without any change in the blood platelets. Pfeiffer and Hoff¹⁸ bled 2 men 50 cc. daily for 5 or 6 days without alteration of the blood platelet level. It would thus seem that the postmenstrual rise in blood platelets cannot be explained on the basis of blood loss.

The variations in the blood platelet count in relation to the menstrual cycle demonstrated in the present investigation suggest a relationship with sex hormones. The question of hormonal control of the platelet level is not new. Schröder,²⁰ on the basis of clinical observations, felt that female sex hormones given in large doses inhibited the function of the bone marrow. Zondek and Kaatz²³ could find no change in the platelet count in patients given estrin and progestin. These observations were limited. Benhamon and Nouchy⁴ were unable to demonstrate a change in the number of blood platelets after the injection of folliculin. Sakai¹⁹ claims there is a stimulation of the function of the reticulo-endothelial system during menstruation. Hirsch and Hartmann¹² were unable to produce alterations in the platelet count in rabbits with the injection of "ovo- and luteo-glandol." Bankow² produced a reduction in the number of blood platelets in white rats after castration. Pfeiffer and Hoff¹⁸ theorize that the corpus luteum hormone influences the spleen so as to prevent out-pouring of platelets. Recently Arnold, Holtz, and Marx¹ have reported the production of an experimental Werlhof's disease in dogs by the administration of large doses of Progynon B-oleosum or the ovarian panhormone of Henning. If the drug was stopped early in the disease, the animals recovered. If the drug was continued, the thrombopenia persisted and the animals died from hemorrhages.

The significance of a premenstrual decrease in the platelets is problematical. Some investigators prefer to look upon it as a periodic latent hemorrhagic diathesis. It may be one of several factors that has led to the general impression that certain women bruise more easily towards their menstrual period. It may be a factor in certain cases of so-called "vicarious" menstruation where misplaced endometrium cannot be demonstrated. Cases of intermittent idiopathic thrombocytopenic purpura related to menstruation may be an exaggeration of this apparently physiologic cyclic process.

✓ **Conclusions.** 1. The determination of the number of platelets by direct counts on capillary or venous blood, with the aid of a satisfactory diluting fluid, is a useful and accurate method. Platelet counts on venous blood average 15% higher than those on capillary blood.

2. The average number of blood platelets in 13 normal women observed during a total of 82 menstrual cycles varied in a regular manner in relation to the menstrual cycle. This change was characterized by a slow progressive decrease during the 14 days prior to menstruation and a rapid increase soon after the onset of the menses. In individual cases there was usually either a slow progressive premenstrual decrease or a rapid decrease immediately before menstruation. In a few instances there was little or no cyclic change in the platelet count and rarely a premenstrual increase occurred.

The author gratefully acknowledges the assistance of Miss Elizabeth King.

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THE PRESENT INCIDENCE OF TRICHINELLA SPIRALIS IN MAN AS DETERMINED BY A STUDY OF 1060 UNSELECTED AUTOPSIES IN ST. LOUIS HOSPITALS.*

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ALL life is apparently subject to parasitism and man is no exception to this general rule, for he has suffered the torment of various

* The author is indebted to Paul A. Wheeler, M.D., Resident Pathologist, St. Louis City Hospital, for his assistance in obtaining material for this study.

parasites from the most ancient times to the present day. It has been claimed that the Mosaic injunction regarding pork was due, in some measure at least, to an infestation of the swine of that period with *Trichinella spiralis*. Be this as it may, the first description of this parasitic worm appeared only a little over a century ago.

Tiedemann, in 1822, probably saw the calcified larval forms of the *Trichinella spiralis* in the muscle tissue of his cadavers. He encountered this condition so often, however, that he regarded the calcified flecks in the muscles as mere "pathological curios" and of no practical importance. Thirteen years later (1835), James Paget,⁷ then a medical student, saw these calcified bodies in the dissecting room material at St. Bartholomew's Hospital. He examined them under the microscope of Robert Brown, the botanist at the British Museum, and discovered that these white specks in the muscles represented a calcified capsule enclosing a coiled up roundworm. His friend and teacher, Richard Owen, reported the discovery to the Zoölogical Society and named the worm *Trichina spiralis*. Due to confusion with another parasite the term was later changed to *Trichinella spiralis*. Zenker¹⁶ was the first to recognize the condition of trichinosis (*i. e.*, trichiniasis) in a girl 19 years of age, who died of what was thought to have been typhoid fever. He found the adult trichinellæ in the intestine and the larvæ in the muscles but not the lesion of typhoid. Virchow¹³ and Leuckart,⁴ working independently demonstrated the relation of the adult intestinal worm to the larval form in the muscles by feeding the latter to animals. Leidy,³ of Philadelphia, in 1847, found the *Trichinella spiralis* in pork which brought to light the importance of this parasite as a public health problem.

The main purpose of the present study was to determine as accurately as possible the extent to which man is, at the present time, infested with *Trichinella spiralis*.

Method. Muscle tissue from 1060 unselected autopsies at Barnes and St. Louis City Hospitals was examined for trichinella larvæ. All of the subjects were over 15 years of age and had died during hospitalization from some disease other than trichiniasis. At autopsy, generous samples of the muscles of election for trichinella, namely, the diaphragm, intercostals, pectorals and recti, were removed and stored on ice in a fresh state if the examination could not be carried out at once. From this material, compression sections were prepared by squeezing thin slices of muscle tissue between two pieces of plate glass in a compression frame (Fig. 2). These fresh unfixed and unstained preparations were then examined microscopically in a methodical manner so that every field in a specimen came into view. Over 12,000 examinations of this type were made during the course of this study in addition to an examination of the usual stained histologic sections (Fig. 3).

Out of 1060 autopsies upon the bodies of individuals never suspected of having trichiniasis during life, 163 (15.37%) nevertheless showed the presence of trichinella larvæ in the muscles. The para-

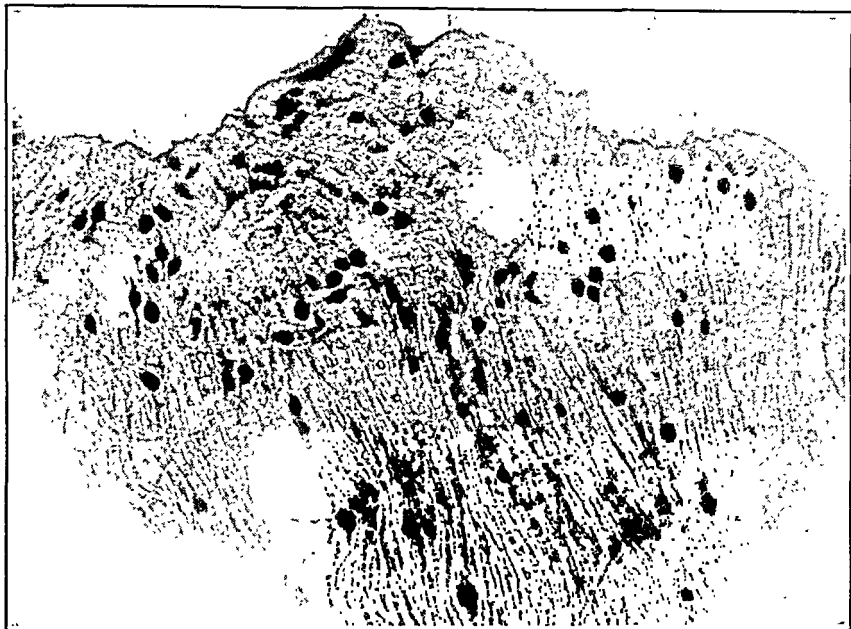


FIG. 1.—Specimen of unstained infested human muscle in compression frame, showing numerous calcified trichinella larvæ. ($\times 10$.)

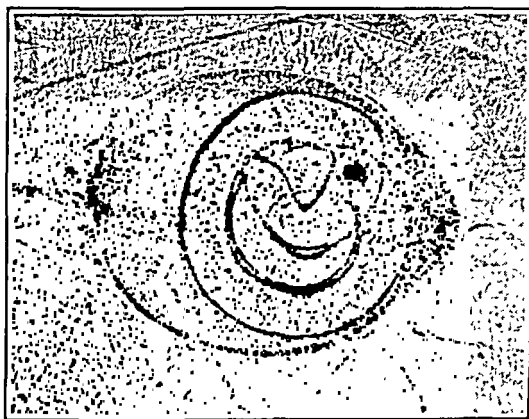


FIG. 2.—Coiled larva within capsule. The dark areas at either end represent beginning calcification. Unstained compression preparation. ($\times 200$.)

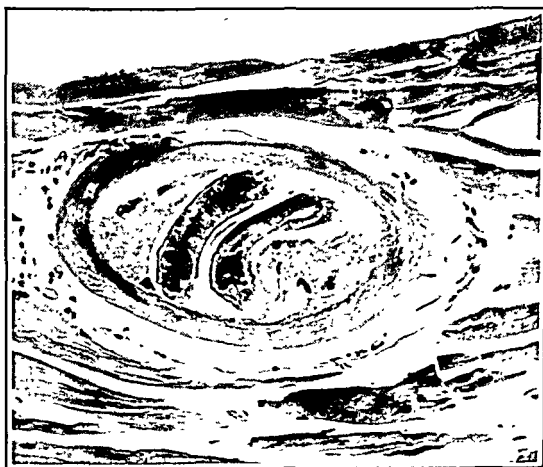


FIG. 3.—Histologic section of encapsulated larva stained with hematoxylin and eosin. ($\times 200$.)

sites were apparently dead in 95% of the cases. In 2 subjects, one 17 and the other 19 years of age, the trichinellæ were completely calcified. On the other hand, in some cases the parasites moved vigorously and often continued to show signs of life for 1 to 6 days after the muscle had been removed. The presence of live parasites was also demonstrated by feeding infested muscle to white rats and recovering the larval forms at the end of 40 days. By these means 5% of the positive cases were shown to contain viable parasites.

TABLE 1.—DEGREE OF INFESTATION OF 163 CASES SHOWING TRICHINELLA SPIRALIS.

Degree.	No. of cases.	Per cent.
Heavy (numerous parasites in every microscopic field*)	18	11.0
Moderate (averaging 1 parasite per 10 fields)	80	49.1
Light (1 or 2 parasites in 50 fields)	55	33.7
Slight (a few found after long search)	10	6.1

* A low-power microscopic field was obtained with a 16 mm. objective and 5X ocular.

The degree of infestation was estimated by comparing the relative number of parasites found in the different cases.

The age of distribution among the 163 cases of infestation is shown in Table 2.

TABLE 2.—AGE DISTRIBUTION AMONG 163 CASES OF TRICHINELLA INFESTATION.

Age group, yrs.	No. of cases.	Per cent.
15 to 30	16	9.2
21 to 50	46	28.0
50 and up	101	61.9

The youngest member of the group was 17 years of age and the oldest 85. Since this is a condition in which chance contact with the parasite determines infestation, it is to be expected that the largest number of positive cases will be found in the higher age groups.

The relation of occupation to infestation is summarized in Table 3. No significant association with any line of work is however apparent.

TABLE 3.—OCCUPATION OF 163 CASES OF TRICHINELLA INFESTATION.

Occupation.	No. of cases.	Per cent.
Industrialists	52	35.0
Agriculturists	37	25.0
Professional	30	20.0
Business	30	20.0

The distribution according to sex showed almost twice as many males to be infested as females. This is of no significance because in the entire group of 1060 cases studied the males outnumbered the females by almost 2 to 1.

The number of foreign-born individuals in the group studied was small so that no definite correlation is evident between the rate of infestation and nationality.

TABLE 4.—INCIDENCE OF INFESTATION DURING THE PAST 50 YEARS.

Author.	Date.	City.	No. of examina- tions.	No. of positive.	Per cent.
Glazier ¹	1881	New York City	150	3	2.0
	1881	Newark, N. J.	100	1	1.0
	1881	Philadelphia	40	1	2.5
Whelpley ¹⁴	1891	St. Louis	20	1	5.0
Thornbury ¹²	1894	Buffalo	21	3	14.3
Osler ⁶	1898	Baltimore and other cities	1000	6	0.6
Williams ¹⁵	1901	Buffalo, Philadelphia, Baltimore and Denver	505	27	5.3
Total for 20-year period 1881 to 1901			1836	42	2.3
Simonds ¹¹	1910	St. Louis	100	2	2.0
Queen ⁸	1931	Rochester, N. Y., and Boston	402	75	18.7
Riley and Scheif- ley ⁹	1934	Minneapolis	167	30	18.0
McNaught and Anderson ⁵	1936	San Francisco	200	48	24.0
Hinman ²	1936	New Orleans	200	7	3.5
Pote	1937	St. Louis	1060	163	15.4
Total for past 27 years			2129	325	15.3

Recent reports have shown a much higher percentage of infestation than the older studies had indicated. During the 20-year period from 1881 to 1901, examinations were made by different investigators on muscle tissue obtained from 1836 autopsies, and only 42 of these were found to be infested (2.28%). During the past 27 years, the number of cases examined was 2129, of which 325 were found to be infested (15.26%). Table 4 summarizes most of the studies made in the United States since 1881.

Discussion. From the publication of Queen, Riley, McNaught and Anderson, as well as the series here reported, it would appear that the incidence of trichinella infestation has greatly increased during the last decade. In 1931, Queen found the infestation rate to be 18.6%. He did not employ the usual compression method with direct microscopic observations, but digested 50 gm. of muscle tissue and detected the parasites in the sediment after digestion. McNaught and Anderson, employing the same technique, reported an infestation of 24%. Hinman digested only 10 gm. of muscle from each case and found 3.5% positive. The increased incidence of *Trichinella spiralis* in man reported since 1931 cannot be attributed to the use of the newer method of digestion. Employing the older technique of microscopic examination of compressed muscle, Riley and Scheifley found 17.9% of specimens positive and the

author's series showed 15.3%. The results obtained by the two methods are close enough to indicate that either technique when properly employed is entirely adequate. The lower percentage of positive results in the earlier reports may have been due, in part at least, to the fact that the number of compression specimens examined was not large enough to detect slight degrees of infestation.

It has often been observed that a severe degree of infestation may exist without related clinical symptoms and in individuals whose history records no incident which might be interpreted as an attack of trichiniasis. Such was the case in each of the 163 positive observations made in this series. The heaviest degree of infestation was in a woman, aged 84, who died as the result of a fracture of the neck of the femur.

During the last 5 years while this investigation has been in progress, only 7 cases of trichiniasis have been reported to the health department in this area. All of these cases have been personally investigated, and it was found that 2 could be definitely accepted, while in the remaining 5 the diagnosis was questionable. This is in agreement with the absence of a clinical history of trichiniasis in practically all of the reported instances of infestation observed at autopsy. A critical study of the clinical history of each of the 163 positive cases in this series reveals that the infestation neither seriously affected the health of the individual nor influenced the course of the terminal illness.

It is disconcerting to realize that at least 15% of the adult urban population is probably infested with *Trichinella spiralis*, in spite of the emphasis which has been placed upon meat inspection during the past 40 years. As the result of a long experience with meat inspection, the author is of the opinion that the least likely source of the parasite is pork products prepared under Federal or adequate Municipal supervision. The incidence of infestation in hog carcasses prepared under Federal supervision in this area is extremely low. Examination of muscle tissue from 1500 carcasses prepared under such supervision during the last 15 years showed only 0.8% to be positive. In packing-houses operated under Federal supervision, all pork products which are apt to be consumed without cooking are processed to destroy the trichinella. About 50% of pork products go to the consumer in the raw state to be cooked before eating.

It has been adequately demonstrated that no practical method of meat inspection can protect the consumer from the possibility of contracting trichiniasis if unprocessed products are not thoroughly cooked. Studies in Germany¹⁰ have shown that about 32% of the cases of trichiniasis occurring between 1881 and 1898 were due to pork products which had been examined microscopically and reported uninfested.

The most frequent source of trichinella in the author's opinion is the unprocessed pork products, especially summer sausage, prepared without supervision in small local slaughter-houses or on farms. Several recent outbreaks of trichiniasis have been traced to such sources.

In the end the final responsibility for the prevention of trichiniasis rests with the consumer, who should be admonished to avoid pork products not prepared under adequate supervision and warned to thoroughly cook all pork.

Summary. Muscle tissue from 1060 unselected autopsies were trichinous to the extent of 15.4%. There had been no symptoms suggesting trichinella infestation.

Ninety-five per cent of the infestations were dead, calcified and more or less disintegrated; 5% were demonstrated to be alive by feeding the infested material to rats and recovering live trichinella larvae.

Very heavy infestations were to be observed where the individual gave a history of having always enjoyed good health. In 1 patient, dying at the age of 84, as the result of an accident, autopsy did not show that the infestation had contributed to the cause of death.

In 1500 hog carcasses examined for trichinella, 0.8% were found to be infested, which gives rise to the question whether man is getting all of his trichinella infestation from pork. It may be concluded that man's infestation comes from pork derived from the small packing plants, which are not supervised by meat inspection services. It is to be noted that the infestations that sporadically occur are from pork from the establishments not under Federal inspection.

Conclusions. It can be very definitely concluded that the *Trichinella spiralis* infestation of man is not a serious lethal factor in Missouri, since in 163 instances of infestation it was not held to have been the cause of death or to have contributed to the cause of death.

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THE EFFECT OF INDUCED HYPERPYREXIA ON THE UREA CLEARANCE OF RHEUMATIC PATIENTS.

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DURING the past few years the use of induced pyrexia in the treatment of certain disease conditions has become increasingly common. Various studies have been made of the physiological and biochemical changes resulting from artificial fever.^{3,4} Further analysis of the effects of induced fever on different bodily functions and organs seems indicated since fever therapy is a strenuous procedure, and proper selection of patients is necessary to avoid untoward reactions. Since artificial fever therapy is still in the investigative stage, criteria for the use of and for contraindications to this type of treatment have not been completely worked out. The present study was undertaken to determine the effect of this sudden increase in body temperature upon renal function, as measured by the urea clearance. No other renal function tests were performed.

Method. Seven patients on the rheumatic fever service of this hospital, who had been selected for this treatment, were observed. All seemed to be in good condition, after allowances were made for their specific disabilities. Artificial fever was induced by placing the patient in a cabinet heated by five 200-W. carbon filament lamps. Only the patient's head and neck protruded from the cabinet, and a minimum of clothing, such as shorts and brassières, were worn, since direct radiant heat on the body hastened the rise of fever. Sedatives, usually nembutal, were given when necessary. Fluids such as water, fruit juices, ginger ale and broth were given as desired by the patient. In addition, all but 2 of the patients received ample quantities of sodium chloride by mouth, either in broth or in a 1% saline solution, in order to replace salt lost through sweating. Continuous temperature recordings were made by a rectal thermocouple and a Leeds and Northrup recorder. The temporal arterial pulse was recorded every 10 or 15 minutes or oftener if excessive tachycardia (above 150) or irregular pulse developed.

A satisfactory treatment was one in which an average rectal temperature of 105° F. was maintained for 5 hours. In some of the first treatments the desired level of 105° was not attained. About 1½ to 2 hours were required to reach this level, after which time the electric current through the lamps was reduced to maintain a fairly constant degree of fever.

Of the 7 patients receiving a total of 14 hyperpyrexial treatments, 2 had rheumatic fever, 3 had subacute or chronic infectious arthritis, 1 had gonococcal arthritis, and 1 had dermatomyositis. Both of the rheumatic fever patients had well-compensated cardiac valvular

TABLE 1.—DATA ON THE EFFECT OF INDUCED FEVER ON THE UREA CLEARANCE OF 7 PATIENTS.

Patient.	Date.	Time in min-utes.	Urine volume, cc. per min.	Urine volume corrected, cc. per min.	Blood urea ni-trogen, mg. per 100 c.c.	U/B.	Urea clearance, % normal.	Average.	Beginning of period.		End of period.		Highest.		Approximate av. temp.	Change in body wt. during treatm't, kg.	Comment.
									Temp.	Pulse.	Temp.	Pulse.	Temp.	Pulse.			
B. B. ♀ 18 yrs. Gonococcal arthritis	9/26/36	77	0.53	0.57	11.00	53.6	75.2		104.0	140	104.5	136	104.8	150	104.0	-0.1	Treatment well tolerated until menses began.
	10/2	249	2.03	2.18	32.6	94.9	85.0	100.4	108	106.1	153	105.0	+1.7	Treatments all well tolerated.
		116	0.48	0.52	79.7	106.3	96.5	104.0	120	105.8	128	104.5	124			
	10/6	160	0.53	0.57	72.2	101.0		105.0	126					
	10/9	66	1.38	1.48	9.00	46.7	105.3			Control							Pt. out of box part time this period.
	10/9	102	0.49	0.53	12.92	63.5	85.4	98.4	103.5	136	105.8	142	106.7	158	105.5	+1.7	
		253	0.51	0.55	66.8	91.9	88.6			102.0	102					
E. F. ♂ 17 yrs. Rheumatic fever	5/29/35	75	0.24	0.25	10.03	72.4	66.4	103.5	152	104.8	148	106.0	152	-1.2	Pt. unable to void again for 13 hrs. Nausea and vomiting. No salt given.
	7/1	65	1.14	1.16	10.47	50.6	101.2	89.2	Control		Control						
		60	3.92	4.00	14.5		77.2									
S. S. ♂ 11 yrs. Rheumatic fever	6/19/35	60	0.27	0.33	10.26	44.7	47.7		103.8	142	105.5	144	105.5	148	105.0	+0.5	Treatment well tolerated. No salt given.
	7/1	102	0.78	0.97	18.2	33.3	40.5			105.2	146					
		60	0.83	1.03	9.22	77.6	146.2				Control						
		60	1.58	1.97	47.7	123.8	135.0									
W. L. ♂ 17 yrs. Chronic infectious arthritis	11/1/35	60	0.27	0.25	15.10	21.8	20.3		106.3	164	105.2	160	106.3	164	105.0	-0.5	Treatments well tolerated. Moderate restlessness. Salted chicken broth given.
	11/5	118	0.56	0.53	63.6	85.8	53.0			105.2	146					
		59	1.24	1.17	12.17	66.5	133.3			Control							
	11/7	60	6.00	5.70	14.2	107.8	120.6									
	11/7	65	0.43	0.41	15.27	39.6	46.9	58.7	106.5	136	106.0	144	106.5	156	105.5		
		60	0.53	0.51	53.4	70.4				104.5	140					

L. S. ♀ 26 yrs. Dermato- myositis	2/7/36 2/11 3/13 3/19 3/21	100 145 60 60 175 724 176 114 60	0.50 0.52 3.63 12.46 0.80 0.39 0.44 0.35 1.03 7.17	0.53 0.55 3.85 13.20 0.87 0.42 0.48 0.38 1.12 7.80	8.27 ... 9.16 ... 13.16 ... 11.45 ... 10.61 ...	57.0 94.7 21.0 6.0 17.4 ... 65.1 ... 57.8 ...	75.5 130.5 108.0 105.0 30.0 10.8 83.8 102.5 113.4 93.0	103.0 106.5 20.4 93.2 103.2	106.3 106.0 106.0 104.0	156 Control 142 132 Control	106.0 105.2 Control 105.8 98.6 105.7 104.7 Control	148 144 140 72 136 130	106.3 160 105.8 105.0	+0.4 +0.1 -0.9	Treatments well tolerated. Saline given. Pt. unable to void for 12 hrs. Treat- ments preceded by hot bath to produce prelim- inary fever. Pt. ex- hausted, nausea and vom- iting. Heat not well tol- erated.
V. S. ♀ 44 yrs. Atrophic arthritis	4/8/36 4/11 4/13	60 105 175 60 60 58 274	1.50 0.30 0.67 2.10 5.50 1.29 0.30	1.58 0.32 0.71 2.21 5.79 1.36 0.32	13.09 14.87 ... 14.87 ...	15.7 31.3 16.0 20.7 13.3 20.6 35.0	36.6 32.9 25.0 60.9 102.8 44.5 36.6	34.8 81.8 40.5	102.5 103.0	124 Control 120	105.5 105.5 Control 105.0 98.6	144 144 130	106.3 106.3 138 104.0	+0.4 104.0	Pt. not coöperative, treat- ment not satisfactory. Pt. complained more than average.
D. S. ♂ 20 yrs. Subacute infectious arthritis	1/7/36 1/14 1/16	229 95 60 58 305 120	0.93 3.05 1.62 1.98 1.61 4.67	0.89 2.93 1.55 1.90 1.54 4.48	14.16 ... 10.69 ... 9.68 ...	46.8 24.9 48.1 40.7 38.3 13.9	81.7 97.1 111.0 104.0 88.0 82.8	89.4 107.5 85.4	105.0 103.8	146 140 out of box	105.5 105.5 105.5	152 140 box	106.5 105.5 160	+3.1 +1.4	Treatment well tolerated; 24 hr. fluid intake 10,980 cc. and 10,350 cc. respec- tively; 4000 and 2000 cc. of 1% saline given during 2 treatments. Pt. out of box at end of 1st period and nearly normal. Un- able to void during treat- ment.

Average urea clearance: First fever period = 61.7; first control period = 109.8. Second fever period = 75; second control period = 100.

lesions. Objectively, all treatments were well tolerated, and except for mild hysteria during two treatments no untoward symptoms were noted.

The clearances were begun after the patient's temperature had been increased to about 104° F. At this time a urine specimen was obtained. The first clearance period generally lasted from this time until the temperature reached its maximum. The second period roughly covered the time during which the temperature remained at its highest point. It was not always possible for the patient to void when asked, because of the profuse loss of water by sweating, so in many instances the first period included part of the time the patient was showing the maximum temperature. Blood was obtained at the end of the first period.

Results. The data thus obtained are shown in Table 1. The average urea clearance during the period when the temperature was rising was 61.7% of normal, and during the period when the temperature was at a maximum the clearance averaged 75% of normal. In 2 instances (E. F. and L. S.) a severe oliguria resulted from the treatment, and these patients were only able to void after 12 hours. For the entire group the average control clearance was 105% when the patients were afebrile.

Discussion. The effect of high artificial fever on dogs has been studied by Knudson and Schaible,³ who found a marked decrease in blood volume. They attributed this to fluid loss, which seems reasonable since they gave their animals no fluid. This dehydration factor consequently obscures the effect which the temperature elevation exerted itself, and it seems likely that the blood changes they noted were due chiefly to desiccation. Moen, Medes and Chalek⁴ observed dogs with artificially induced fever in which attempts were made to overcome the dehydration factor. They noted only minor changes in both total plasma protein and the plasma-protein fractions of these dogs. No data were given concerning non-protein nitrogen.

In patients with Bright's disease in this clinic, a significant direct relationship between fever and the urea clearance has not been noted. Goldring² found the urea clearance slightly elevated in active febrile rheumatic fever; and Farr and Abernethy¹ found a marked elevation of the urea clearance in pneumonia which was not related to temperature. On the other hand, Page⁵ found no change in urea clearance during diathermy treatment applied locally over the kidney region.

In dogs, Van Slyke, Rhoads, Hiller and Alving⁶ found the urea clearance varied in direct proportion to the renal blood flow. In our patients the mechanism producing the lowered clearance was presumably a retarded renal blood flow. Possible causes of the retarded renal circulation may have been either deflection of blood from the kidneys to the hyperemic skin,³ or occurrence of some desiccation⁴

despite the precautions taken to prevent it. The decrease in renal function was not serious in any of our patients, and was transitory. The fact that a definite decrease occurred, however, emphasized the desirability of combating desiccation during the febrile treatments, and of applying them with caution to patients with damaged kidneys, until their effects in such patients have been studied.

Summary. Urea clearance tests were done on 7 patients before, during, and after hyperpyrexia was artificially induced.

The average urea clearance was 61.7% of normal during the period when the fever was mounting, and 75% when the fever was maintained at its maximum. The control clearances on these patients averaged 105% of normal.

The data indicate the desirability of combating dehydration during fever therapy.

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THE EFFECT OF BENZEDRINE, BENZEDRINE AND ATROPINE, AND ATROPINE ON THE GALL BLADDER.*

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THE physiologic actions of benzedrine sulphate (phenylisopropylamine sulphate) are primarily those following stimulation of the sympathetic division of the autonomic nervous system.^{1-13,15,16} In the gastro-intestinal tract it has been demonstrated that benzedrine increases the acidity and pepsinogen of the gastric juices,⁹ and decreases the tonus of the entire gastro-intestinal tract.⁷

Because of the relaxation obtained by the use of benzedrine in the gastro-intestinal tract we have decided to extend our work on benzedrine to cover the total digestive apparatus, and in this particular instance to investigate the effects of benzedrine upon the gall bladder. In a preliminary study,¹⁴ we found that the gall bladder emptied normally when a fatty meal was administered within

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$\frac{1}{2}$ hour after the benzedrine, but that it failed to empty when a fatty meal was given at least 2 hours after the drug. The observation⁸ that paralysis of the parasympathetic nervous system by atropine enhanced the effect of benzedrine on general body physiology has stimulated the additional investigation of the effect of the combination of benzedrine and atropine on the gall bladder. To complete our study, the effect of atropine alone on the gall bladder was carried out. It is the purpose of this paper to present these observations.

Method. The individuals used in this work were all mentally ill but physically normal. They coöperated well throughout the period of the study. All were males with an age range of 32 to 51 years. Each patient was used as a control on himself and on the entire group.

Control Study. Before the benzedrine study was started each patient received a gall bladder dye test to determine the size and rate of emptying of this viscus. The night before the test the patient received a light meal consisting of dry toast, tea and sugar. One hour later he was given the gall bladder dye, tetro-iodo-phenolphthalein sodium, orally. The following morning, after a fast of at least 15 hours, Roentgen ray films were taken of the gall bladder region. Then he was given a meal rich in fat, consisting of two slices of white bread thickly spread with butter, and 2 glasses of milk and cream mixture into which had been beaten 4 raw eggs. After a lapse of 1 to 2 hours Roentgen ray films were again taken. Only those individuals were used in whom there was either a marked diminution or complete disappearance of the gall bladder shadow on the Roentgen ray films taken after the fatty meal. This method of dye administration and type of meal were used throughout the work.

Benzedrine Study. In this series, after initial Roentgen ray films of the dye-filled gall bladder, the patient was given 30 mg. of benzedrine subcutaneously. One-half hour later, films were taken and the patient immediately given a fatty meal. Films were then repeated at 30 and 60-minute intervals.

Benzedrine and Atropine Study. The same procedure was followed as in the benzedrine study excepting that atropine, gr. 1/100, and benzedrine, 30 mg., were administered subcutaneously and at the same time.

Atropine Study. Again the same procedure was followed as in the benzedrine study excepting that atropine, gr. 1/100, but no benzedrine, was given subcutaneously.

Each of these procedures was carried out on every patient. Twenty-two such studies were made. The benzedrine was used as benzedrine sulphate, and the atropine as atropine sulphate. The drugs were always given subcutaneously.

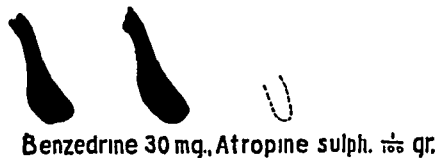
Results. Chart 1 demonstrates the effect of benzedrine, benzedrine and atropine, and atropine on the gall bladder; it also illustrates the ability of these drugs to prevent the emptying of the gall bladder after a fatty meal is given. This chart shows that: 1. The size of the gall bladder is affected very little by benzedrine. In 1 of our cases there was a slight increase in the size of the gall bladder,

LEGEND FOR CHART 1.

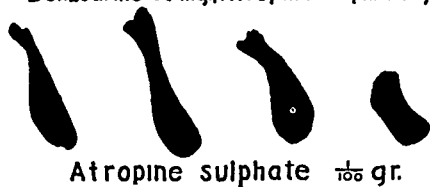
CHART 1.—Changes in the gall bladder shadow following the use of benzedrine 30 mg., benzedrine 30 mg. and atropine 1/100 gr., and atropine 1/100 gr. subcutaneously.

Benzedrine 30 mg.

Before drug $\frac{1}{2}$ hr. after drug $\frac{1}{2}$ hr. after fat meal 1 hr. after fat meal



Benzedrine 30 mg., Atropine sulph. $\frac{1}{100}$ gr.

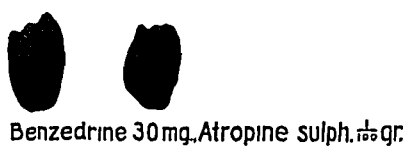


Atropine sulphate $\frac{1}{100}$ gr.

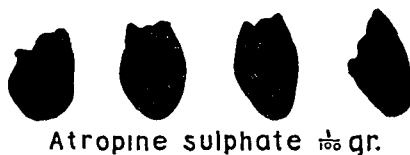


Benzedrine 30 mg.

Before drug $\frac{1}{2}$ hr. after drug $\frac{1}{2}$ hr. after fat meal 1 hr. after fat meal



Benzedrine 30 mg., Atropine sulph. $\frac{1}{100}$ gr.



Atropine sulphate $\frac{1}{100}$ gr.



Case 2

Benzedrine 30 mg.

Before drug $\frac{1}{2}$ hr. after drug $\frac{1}{2}$ hr. after fat meal 1 hr. after fat meal



Benzedrine 30 mg., Atropine sulph. $\frac{1}{100}$ gr.



Atropine sulphate $\frac{1}{100}$ gr.



Case 8

Benzedrine 30 mg.

Before drug $\frac{1}{2}$ hr. after drug $\frac{1}{2}$ hr. after fat meal 1 hr. after fat meal



Benzedrine 30 mg., Atropine sulph. $\frac{1}{100}$ gr.



Atropine sulphate $\frac{1}{100}$ gr.



Case 20

Benzedrine 30 mg.

Before drug $\frac{1}{2}$ hr. after drug $\frac{1}{2}$ hr. after fat meal 1 hr. after fat meal



Benzedrine 30 mg., Atropine sulph. $\frac{1}{100}$ gr.



Atropine sulphate $\frac{1}{100}$ gr.



Case 22

Benzedrine 30 mg.

Before drug $\frac{1}{2}$ hr. after drug $\frac{1}{2}$ hr. after fat meal 1 hr. after fat meal



Benzedrine 30 mg., Atropine sulph. $\frac{1}{100}$ gr.



Atropine sulphate $\frac{1}{100}$ gr.



but this was not striking. The gall bladder emptied after a fatty meal in every instance but one. In this case there was a very definite retardation of the emptying time even after 1 hour and it was felt that this delay was probably due to the drug.

2. When atropine was used in addition to the benzedrine the gall bladder shadow increased somewhat in size in 3 cases and decreased in size in 1 case. These alterations were not marked but were more definite than when benzedrine alone was used. After the fatty meal, however, there was a very definite delay in the emptying of the gall bladder. Although in every case but one (Case 7) there was some decrease in the size of the gall bladder shadow, this decrease did not by any means eradicate the clearness of this shadow. In 1 case (Case 8) the shadow did become progressively smaller so as to approximate normal emptying.

3. The use of atropine alone produced little or no change in the size of the gall bladder shadow excepting in 2 cases (Cases 2 and 7) where there was a definite increase in the size of the gall bladder. After the fatty meal had been given the gall bladder emptied in only 1 case (Case 1). In all of the other patients the size of the gall bladder shadow remained approximately unchanged and the retention of the dye within this viscus was quite definite.

Discussion. The mechanisms whereby the gall bladder is able to empty itself or be emptied have been ably discussed by Ivy. They resolve themselves into: *a*, direct stimulation of the walls of the gall bladder physically or chemically; and, *b*, indirect stimulation physically and chemically through the autonomic nervous system. Although benzedrine sulphate is a drug capable of stimulating the sympathetic division of the autonomic nervous system, it is not at all certain that the gall bladder effects as observed in our previous study and in this paper are due to this power of the drug. The physiologic (autonomic) effects of this drug are at their height before 30 minutes and most of them have worn off in 1 hour. Still when a fatty meal is given $\frac{1}{2}$ hour after the drug there is a normal emptying response of the gall bladder to the meal, but when the drug was permitted to act for 2 hours and then a fatty meal given, there was a definite retention of the dye in the gall bladder. If we assume that the action on the gall bladder is due to sympathetic stimulation then we must assume that some mechanism is set up which causes a delay in the establishment of such stimulation. Whether this delay is due to the retarded progress of the fatty meal into the duodenum because of the decreased motility of the stomach or to some other mechanism is not known at the present time. We do know that when the motility of the stomach is diminished by use of atropine there is a definite delay in the emptying of the gall bladder. However, the authenticity of this was questioned when it was found that atropine alone will produce a delay in the emptying of the gall bladder. Further work will have to be conducted before these points are definitely clarified.

The observations of Myerson that paralysis of the parasympathetic system by the use of atropine apparently enhances the action of the sympathetic stimulant benzedrine suggests a constantly active system of checks and balances existing between the sympathetic and parasympathetic systems. He states that when the sympathetic division of the autonomic nervous system is stimulated, as by benzedrine, a complete effect may not be obtained because of the continued activity of the parasympathetic division and that when the latter is paralyzed the complete effect is obtained. His conclusions are not borne out in our studies on the gall bladder. In these it would appear that the benzedrine interfered with the effect on the gall bladder obtained by atropine; that when atropine alone was used a better retention was obtained than when benzedrine and atropine were used.

From these studies it seems that, except in the odd case, benzedrine delays the emptying of the gall bladder only after a long period has lapsed following administration of the drug; and that sympathetic stimulation, if it is effective, occurs only after a prolonged period. It would appear that the combination of a sympathetic stimulant and parasympathetic paralyzant is effective in delaying the gall bladder emptying, but that this effect is not so marked as when the parasympathetic paralyzant, atropine, is used alone. It cannot definitely be stated whether these results are due to direct or to indirect action of the drug on the gall bladder. It seems, however, that although the results obtained by the use of benzedrine are questionably sympathetic, those obtained by use of atropine are definitely due to parasympathetic paralysis. This would indicate that should a drug be desired to relax the gall bladder walls or to inhibit emptying of the gall bladder, a parasympathetic paralyzant would be of greater value than a sympathetic stimulant.

Summary. The results of the effect of benzedrine, benzedrine and atropine and atropine on the gall bladder are presented. The immediate effects of benzedrine on this viscus are negligible; benzedrine and atropine combined definitely delay the emptying of the gall bladder but not as adequately as atropine alone.

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PATHOLOGICAL PHYSIOLOGY OF PULMONARY CYSTS AND EMPHYSEMATOUS BULLÆ.

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KOONTZ¹⁴ first called the attention of the American clinicians to congenital cystic disease of the lung, when he reported a case in 1925 and collected from the European literature 108 additional cases. Since that time numerous case reports have appeared. Most observers have been chiefly concerned with the etiologic factors, pathogenesis, pathologic observations, symptomatology and roentgenographic studies of such anomalies. Investigating a large group of men with chronic respiratory disorders over a period of 3 years, we found 6 individuals whose roentgenograms showed annular shadows of varying size and extent. Our main objectives in making this study were to seek an explanation for the mechanism of dyspnea which appeared to be the cardinal symptom and the chief cause of disability and to determine whether the abnormality was congenital or the result of obstructive emphysema, *i. e.*, emphysematous bullæ.* The majority of the cases herein reported had in addition to the air filled cysts, pulmonary fibrosis or obstructive emphysema. Thus far we have not encountered a case that simulated "honey comb lung" or one that would be confused with congenital bronchiectasis. From a review of the literature there appears to be no uniformity of opinion as to how one can differentiate clinically congenital cystic disease of the lung, congenital bronchiectasis or acquired cavities filled with air resulting from the breakdown of pulmonary tissue. This communication presents the results of a study from the functional viewpoint of 6 cases with cystic changes of the lungs and emphysematous bullæ.

* The term "bulla" is used in this paper as defined by W. S. Miller.^{14a} "A *bleb* was caused by a rupture of the pulmonary alveoli immediately beneath the pleura which allowed air to escape into the pleura and caused it to separate from the underlying alveoli, thus forming a thin-walled space situated outside of the lung itself; while in the case of a *bulla*, although the alveoli beneath the pleura were greatly distended, and eventually by the destruction of the interalveolar walls formed a large space that often projected beyond the level of the surrounding pleura, it was situated within the lung and was covered by the intact pleura. In other words, a *bleb* is an interstitial emphysema situated within the pleura and causes those thin-walled, bladder-like prominences which are found on the surface of the lung, while a *bulla* is due to a vesicular emphysema situated within the lung and though it often projects beyond the surface of the lung is covered by an intact pleura."

Case Reports. CASE 1.—C. D. (No. 52358) was a 35-year-old coal miner who was admitted to the Strong Memorial Hospital November 13, 1933, with the chief complaint of shortness of breath. The patient dated the onset of his present illness to 1917 at which time, while in the army, he had an attack of abdominal pain accompanied by diarrhea of 3 weeks' duration. Since that time there has been a progressive increase in dyspnea and marked constipation. After discharge from the army, the patient continued his usual occupation (coal mining) until 1926, when he had to quit his job for a less strenuous one because of breathlessness. Since the onset of the illness there has been a constant cough productive of thick yellow sputum, never blood tinged and more marked in the morning. In 1918, 1923 and 1925 there were attacks of "bronchitis" with fever and an increase in the productive cough. He had noticed clubbing of the fingers for 20 years. There was a gradual loss of weight from 88.6 kg. in 1917 to 48 kg. in 1933. There was no history of precordial pain, edema or orthopnea. In fact during the 2 years prior to admission he was more comfortable lying flat in bed than in an upright position. Since 1931 he had been practically bedridden because of severe dyspnea.

Prior to 1919 his general health was excellent. As a child he had measles complicated by pneumonia. He worked in bituminous coal mines for 13 years.

Physical Examinations. The temperature was 37° C. The patient was a well developed but undernourished man, who appeared acutely ill. His characteristic position in bed was fully supine with his arms extended above his head grasping the head of the bed. Respirations were rapid (28 per minute) and labored. With each inhalation the inspiratory muscles of the neck were very tense and prominent and the supraclavicular fossæ were markedly accentuated. When the patient assumed the sitting position the respirations became more rapid and dyspnea more marked. Talking and eating greatly accentuated his respiratory distress. The mucous membranes of the lips and eyelids and the finger nail beds were cyanotic. There was marked clubbing of the finger and toes. The chest was symmetrical with an increase in the anteroposterior diameter. The lower part of the chest cage flared moderately. Expansion of the chest was limited bilaterally. All the respiratory muscles were well developed in contrast to the general musculature. The percussion note had a tympanitic quality. The precordial and hepatic dullness was obliterated. Tactile fremitus was poorly transmitted over the whole chest except at both bases where it was increased. The pulmonary bases descended poorly. Over the upper half of both lungs the breath sounds were diminished, while at the bases they were exaggerated and very harsh. The heart could not be outlined by percussion. The rhythm was regular. There were no audible murmurs. The pulse rate was 80 per minute. The blood pressure was 92/70 mm. of mercury. There was no peripheral edema.

Laboratory Data. The red blood cell count was 5.8 millions per c.mm.; hemoglobin, 19 gm. per 100 cc. of blood; white blood cell count, 11,200 with a normal differential count. The blood Wassermann test was negative. Repeated search for acid-fast bacilli in the sputum was negative. The electrocardiogram showed right axis deviation. Roentgenogram of the chest (October 5, 1931 and November 14, 1933, see Fig. 1) showed a large pocket of air in both pleural spaces which extended as low as the sixth interspace on the left and the seventh on the right. The lungs were compressed toward the diaphragm and occupied about one-third of the pleural spaces. There were many small dense calcified areas in both lungs at the level of the ninth and tenth posterior ribs. The heart was normal in size and shape.

Course. On November 15, 1933, a needle was inserted into what was thought to be the right pleural cavity. The pressure was -6 mm. of water at the end of inspiration and $+5$ cm. at the end of expiration. Air (2000 cc.) was removed without change in the symptoms, intrapleural pressure or in the size of the cavity. A like procedure was carried out on the left side with similar results. On December 6, 1933, a thoracoscopy was performed on the left side by the late Dr. E. W. Phillips, for the purpose of locating a pleuro-bronchial fistula. Portions of the lung were found to be of normal pink color and apparently air containing, while other portions were of deep bluish color apparently atelectatic. There were several adhesions passing between the lung and the chest wall and between different portions of the collapsed lung. Still being of the opinion that this was a case of a bilateral pneumothorax with a pleural-bronchial communication, on December 27, 1933, Dr. Phillips performed an exploratory thoracotomy on the left side and found a large air cyst which filled the upper half of the chest. The cyst was removed and the patient died about 2 hours after the operation.*

Clinical Diagnoses. Pulmonary fibrosis, anthracosilicosis; bilateral emphysematous bullæ; congenital cystic disease of the lung (?)

Autopsy (No. A-2476, performed by Dr. Ralph E. Knutti). The heart weighed 260 gm. The right auricle and ventricle were slightly dilated. The most striking feature was the marked right ventricular hypertrophy. The walls of which measured 1.2 cm. in thickness. The left ventricular wall averaged 1.2 cm. in thickness. The myocardium showed no abnormalities. All the valves appeared normal. The coronary orifices were patent. The arch of the aorta had a smooth intimal surface. The coronary arteries were wide and showed in some places, particularly where branches existed some tiny, yellow subintimal plaques. *Lungs:* The left weighed 500 gm. The right was not weighed (see roentgenogram of the right lung after removal, Fig. 2). The left lung had a deep blackish-red color. It was subcrepitant in the central portions of the lobes and crepitant at the margins. The margins showed numerous, quite large (up to 1.5 cm. in diameter) cushiony, thin-walled bullæ. Some of these were single; others apparently represented whole lobules. The central portions of the lobes were partially collapsed, elastic, soft and black in color. There was no consolidation and no resistance to section. No fibrous nodules were noted. The bronchi showed no dilatation. The bronchial mucosa was smooth. The pulmonary arteries showed marked, quite sizable yellow subintimal streaks and plaques. The right lung, at the upper portion of the upper lobe, contained a tremendous, round thin-walled, semi-transparent sac filled with air. It measured 15 by 15 by 10 cm. and was single (Fig. 2). The lung elsewhere showed cushiony emphysematous bullæ at the margins of the lobes, similar to those seen in the left lung. The main portions of the lobes appeared to be partially collapsed. There was no external or palpable evidence of consolidation or nodulation. On section of the right lung, there was a large fibrous walled cyst at the apex with reduction of the upper lobe by about one-half (Fig. 3). The lung tissue formed the lining of the lower part of the cyst and thin interlacing bands of connective tissue stretched out to the walls of the cyst laterally. Throughout the remainder of the lung there was marked emphysema particularly in the lower lobe where several bullæ 2 cm. in diameter were found with adjacent air sacs greatly enlarged. Anthracosis was very marked.

Microscopic Notes. Section through the hilus of the left lung showed marked fibrosis and coal pigmentation. Large lamellated nodules were present, composed of hyalinized connective tissue with calcified centers. In the fibrous tissue about the nodules, there was a tremendous amount of black pigment material. Metaplastic alveolar epithelium was included in

* This patient was kindly referred to us by Dr. John J. Lloyd.

some strands of fibrous tissue. The alveoli outside the most marked fibrotic areas were collapsed. The alveolar walls were markedly infiltrated with coal pigment. The pulmonary vessels showed marked intimal thickening. The bronchi had greatly thickened walls which were infiltrated with chronic inflammatory cells. A section through the lung, away from the hilus, showed a considerable thickened pleura which, in the subepithelial fibrous tissue, showed marked black pigment infiltration. Alveolar epithelium adjacent to this fibrous layer was markedly metaplastic. Alveolar walls were everywhere greatly thickened. Even greatly dilated emphysematous alveoli which were quite numerous, showed walls considerably thicker than those of a normal alveolus. Many of the alveolar walls, especially the thicker ones, near the pleura, which were obviously fibrotic, contained considerable black pigment, most of which was presumably in large mononuclear phagocytic cells. Sections through the main pulmonary arteries showed marked intimal thickening and proliferation with fatty, subintimal plaque formation. Sections through the wall of the large cystic space of the right lung showed a pleura which varied in thickness, but was not, in the section studied, greatly thickened (Fig. 4). It was infiltrated with chronic inflammatory cells and contained black pigment and occasional groups of metaplastic alveolar epithelial cells. The remainder of the wall was composed of flattened alveoli, all compressed in a longitudinal plane; the walls of these were thickened with fibrous tissue. The other showed considerably thinned walls. Those that were considerably thickened were lined with metaplastic epithelium. The inner surface was composed of alveolar walls, some apparently being part of greatly dilated flattened alveoli; others projecting into space, being connected with other walls at the inner surface. Some flattened bronchi with metaplastic epithelium were noted. Sections from other portions of the right lung showed marked emphysema and atelectasis, marked fibrosis with nodular formations of hyalinized lamellated connective tissue and marked dilatation and collapse of alveoli and most marked black pigment infiltration.

Anatomic Diagnosis: Massive emphysematous bullæ, bilateral; pulmonary emphysema and atelectasis; pulmonary arteriosclerosis; pulmonary fibrosis; anthracosilicosis (marked); cardiac hypertrophy, right ventricle; clubbed fingers.

CASE 2.—A. W., was a 55-year-old man who complained of shortness of breath. Because of medico-legal considerations we were unable to obtain a satisfactory history. He was exposed to considerable amounts of dust, some of which presumably contained silica. Dyspnea was produced by the slightest exertion. The roentgenograms of the chest are reproduced in Figures 5 and 6. The chest cage appeared slightly asymmetrical with wider rib spaces on the right, particularly over the lower portion of the right lung. The left leaf of the diaphragm was noted in a low position and sloped gradually to a broad costophrenic angle. The left leaf was somewhat indistinct and the angle on this side was partly obscured. The heart was not enlarged in the posterior anterior projection. However, the pulmonary artery appeared very prominent in both the posterior anterior and lateral projections. The aortic knob was not unusually prominent. The right pulmonary field in general appeared more radiotranslucent than the left. The markings on this side at the infraclavicular level radiated outward without any disturbance in general contour. The lower part of the right lung showed numerous radiotranslucent areas suggesting the presence of air cysts or bullæ. Over the lower part of the right lung the presence of these cysts had disturbed the alignment of the usual linear markings. They have been deflected medially and forward. The lung markings appeared increased. This was apparent over the right lower lung and throughout the left. The hilar structures appeared somewhat prominent. About the upper

pole of the left hilum there were shadows of increased density suggesting fibrosis while at the left pulmonary base the shadows appeared very dense and extended down to the level of the diaphragm. The prominence of the pulmonary artery may be taken as evidence of hypertension of the lesser circulation.

Clinical Diagnoses. Pulmonary fibrosis; congenital cystic disease of the lung.

CASE 3.—J. L. (No. 74455) was a 59-year-old belt cutter admitted to the Rochester Municipal Hospital on April 26, 1933, complaining of shortness of breath for 1 year and asthma of 14 years' duration. He had a chronic cough productive of small amounts of phlegm for 14 years, associated with frequent paroxysms of bronchial asthma. Recently the cough had gradually become worse and for the past year he had increasing dyspnea on exertion without edema or orthopnea.

On *physical examination* the temperature was normal, the pulse 90 and the respirations 20 per minute. The blood pressure was 130/80 mm. of mercury. He was an undernourished man of 59, who did not appear ill. There was slight clubbing of the fingers. The mucous membranes were cyanotic. The thorax was symmetrical with an increase in the antero-posterior diameter. Percussion note had a tympanitic quality. Wheezing breath sounds were heard over both pulmonary fields accompanied by fine scattered crepitant râles over the upper portions of the lungs and moist râles over both bases. The heart was not enlarged. Rhythm was regular except for an occasional extra systole. There was a systolic whiff over the aortic area.

The patient was again admitted to the hospital in July, 1935, at which time the studies reported in this paper were made. At that time he remarked that shortness of breath was more easily induced than formerly, but there were no other symptoms or signs of congestive heart failure.

Laboratory Data. The red blood cell count was 3.45 million; hemoglobin, 10.5 gm. and white blood cell count 7000 with a normal differential count. The blood Wassermann test was negative. The electrocardiogram showed left axis deviation and occasional ventricular extrasystole. Roentgenogram of the chest (July 29, 1935) showed the right upper pulmonary field above the sixth interspace posteriorly to be unusually brilliant. It lacked the usual normal markings seen in the left side. The markings seem to run

LEGENDS FOR FIGS. 1, 2, 5 AND 6.

FIG. 1.—Roentgenogram of the chest of a case (C. D.) of Bilateral Emphysematous Bullæ. Note the marked displacement downward of both hilar structures, the complete absence of all pulmonary markings over the upper portions of the pulmonary fields and the compact character of the markings at the pulmonary bases, many of which describe curved course as a result of pressure by adjacent bullæ.

FIG. 2.—Roentgenogram of the right lung after removal from the thorax (Case C. D.). The large cyst (filled with fixing fluid) is shown in the upper lobe, while many smaller bullæ are seen around the peripheral portions of the lower lobe.

FIG. 5.—Roentgenogram of the chest of Case 2 (A. W.). The right lower pulmonary field shows an area of decreased density over which few pulmonary markings can be outlined. The markings bordering along the upper and medial aspects of this shadow are deflected upward and medially, their normal distribution being disturbed by pressure exerted by cysts. Note also the tilting upward of the interlobar septum between the right upper and middle lobes. On the left side, the changes relate chiefly to fibrosis.

FIG. 6.—Roentgenogram of the chest, lateral view (Case A. W.). The actual borders of several of the larger cysts can be outlined much more clearly in the lateral projection than in the usual postero-anterior film. Note the prominent shadow of the pulmonary artery beneath the aortic arch.



FIG. 1

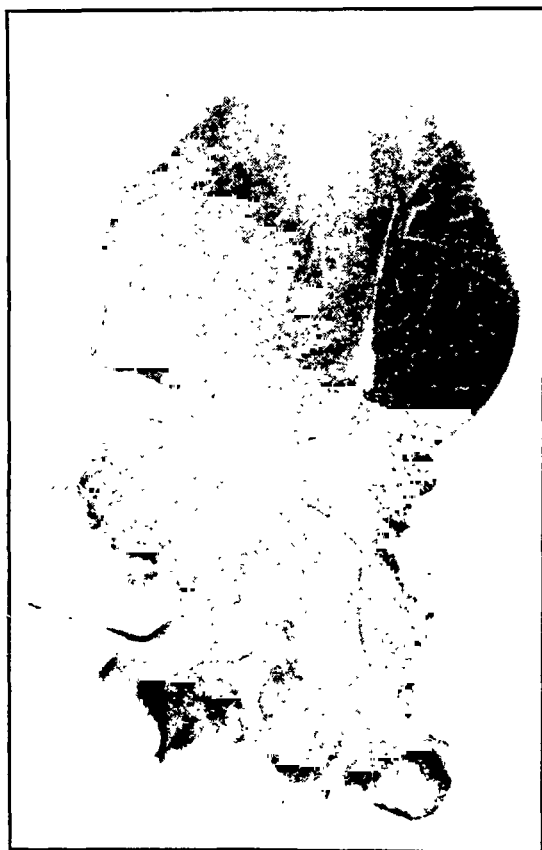


FIG. 2

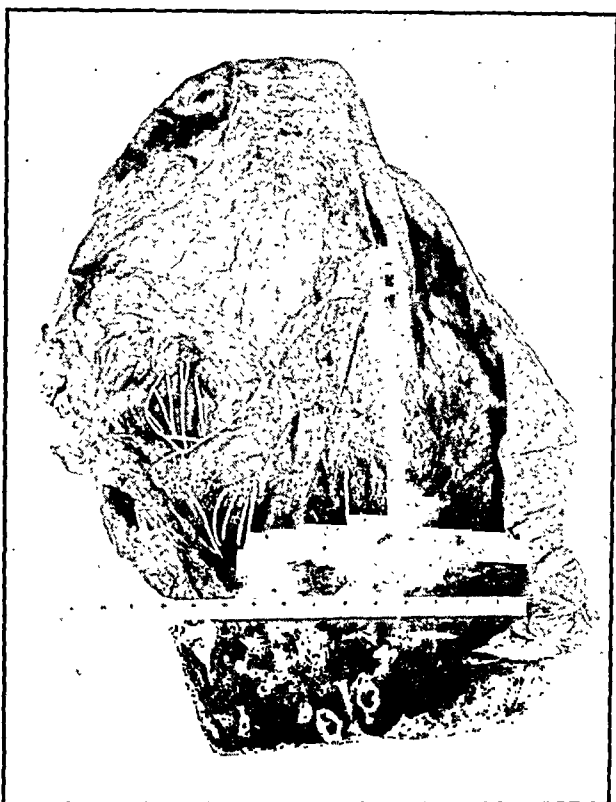


FIG. 3.—Section of the right lung showing the interior of the large emphysematous bulla with several smaller ones. The fine interlacing strands have been retouched.

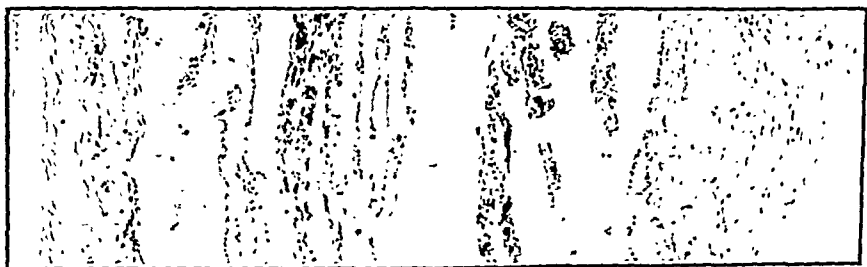


FIG. 4.—Photomicrograph of the wall of the large emphysematous bulla (Case C. D.). Magnification 100 X.

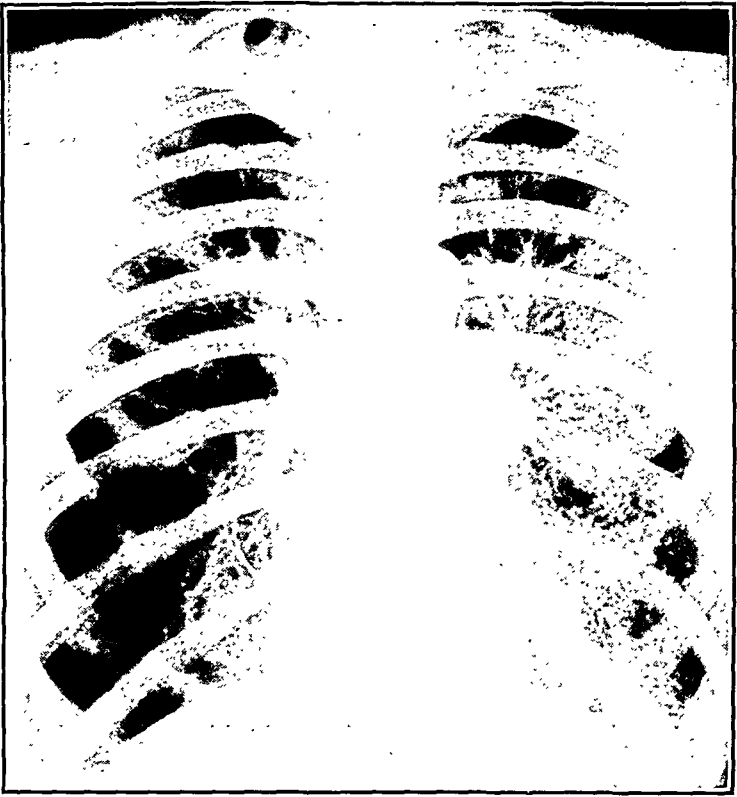


FIG. 5



FIG. 6

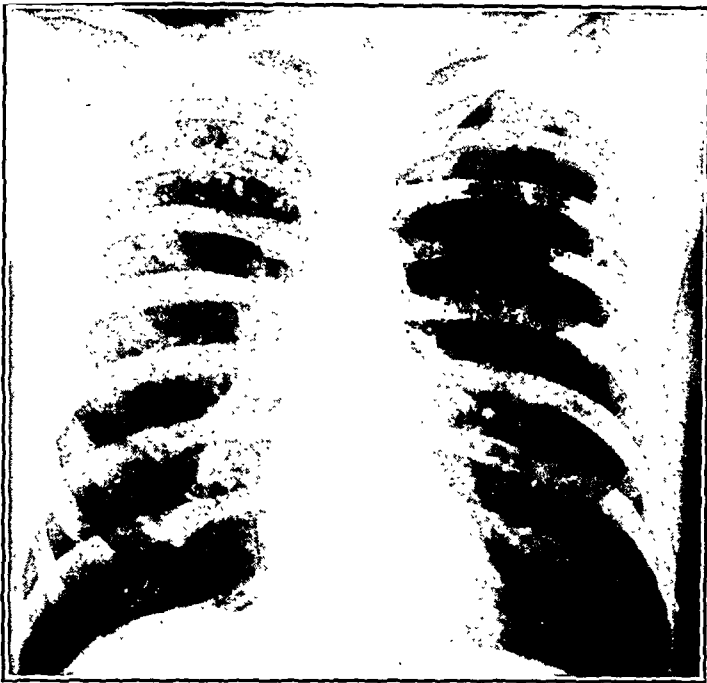


FIG. 7.—Roentgenogram of the chest (Case 5, R. W.). The left pulmonary field appears abnormally brilliant with very few pulmonary markings over its upper portion. The upper pole of the left hilum appears compressed and displaced downward. The densities over the right upper lobe relate to an old minimal tuberculosis with calcification.

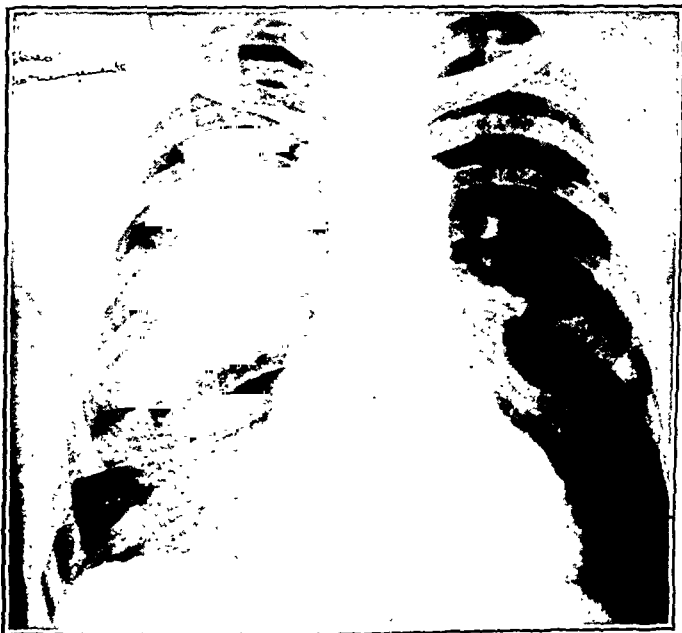


FIG. 8.—Roentgenogram of the chest (Case 6, J. D.). The right pulmonary field of this case is very similar in general appearance to that observed in Case 1: (a) abnormal brilliancy of upper right pulmonary field, (b) absence of the right hilar structure at its usual level, (c) the disturbed curved course of the pulmonary markings at the lower border of this shadow. Note the linear shadow crossing the lower right pulmonary field cast by the interlobar septum. The position of this septum suggests that the right upper lobe occupies at least three-quarters of the entire pulmonary field.

across the pulmonary fields and apparently outlined a large emphysematous bulla. The hilar structures were prominent. The diaphragms were low in position and on fluoroscopic examination the excursions of both diaphragms were diminished. The measurements of the heart were within normal limits. The pulmonary artery was prominent.

Clinical Diagnoses. Obstructive pulmonary emphysema; emphysematous bulla; bronchitis, chronic; asthma, bronchial.

CASE 4.—E. W. (No. 105034) was a 54-year-old laborer who was examined because of a history of exposure to silica. His chief complaints were "asthma" and frequent colds. For many years he had one or two chest colds every winter with right sided pleural pain of 2 or 3 weeks' duration. During these attacks he had a productive cough without fever. He complained of dyspnea on moderate exertion and he had asthmatic attacks for the past 4 years. During the past 12 years he had been working in grinding and mixing mills where he was exposed to considerable amounts of dust. In the past he had pneumonia at 19 years, typhoid at 20 and repeated attacks of sinusitis.

On *physical examination* the temperature, pulse, and respiratory rate were normal. The blood pressure was 110/70 mm. of Hg. The patient was a tall, thin man who appeared chronically ill. There was no cyanosis, clubbing of the fingers or edema. The thorax was of the asthenic type. Inspiratory retraction was marked in both supraclavicular fossæ. The left chest moved better than the right. The bases descended 4 cm. on the right and 6 cm. on the left. The percussion note had a tympanitic quality with dullness in the right interscapular region and right base posteriorly. Breath sounds were vesicular, accompanied by wheezing rhonchi. In the right mid-scapular region bronchial breathing was heard. From this region to the base and in the axilla coarse râles were heard on quiet breathing and after expiratory cough. The heart measured 10.5 cm. in the fifth interspace. The retromammary dullness was 7.5 cm. The rhythm was totally irregular in rate and force. There were no audible murmurs. The radial arteries were markedly sclerotic.

Laboratory Data. The red blood cell count was 5.59 millions; hemoglobin, 14 gm. per 100 cc.; white blood cell count, 11,300 with a normal differential count. The blood Wassermann test was negative. The electrocardiogram revealed auricular fibrillation. Roentgenogram of the chest showed the right diaphragm to be irregular and the costophrenic angle obliterated. Both pulmonary fields showed an extensive diffuse pulmonary fibrosis. On the right side large masses of fibrotic tissue were observed along the right axillary margin and at the level of the right hilus. The upper pole of the right hilus was enormously increased in size and density. The right apex and upper portion of the infraclavicular region on the right side was exceptionally brilliant. The right base showed diffuse fibrosis without the presence of agglomerated masses. On the left side the fibrosis appeared less marked though it extended from the apex to the base. The pulmonary field on this side showed no large fibrotic masses. The left hilus was greatly increased in size and density.

Clinical Diagnoses. Emphysematous bullæ; pulmonary fibrosis; obstructive pulmonary emphysema; heart disease, arteriosclerotic with auricular fibrillation.

CASE 5.—R. W. (No. 101120) was a 39-year-old delivery man complaining of asthma and shortness of breath of 3 years' duration. The present illness began with a "head cold" associated with wheezing respirations. Since that time he had had intermittent paroxysms of asthma during the day and almost constantly at night. Two years before admission he had a purulent sinusitis. During the 3 months prior to admission dyspnea was so severe he had to stop working. In the past he had pneumonia at the age of 28. He had never been exposed to any known industrial hazard.

Physical examination revealed an undernourished man, acutely and chronically ill. He was sitting upright in bed in evident respiratory distress. He had severe paroxysms of cough productive of small amounts of purulent sputum with occasional blood streaking. The mucous membranes were cyanotic. The upper left chest was more prominent than the right with a definite lag on deep inspiration. Expansion of the chest was diminished bilaterally. The percussion note was impaired from the right apex to the third interspace anteriorly and to mid-scapular area posteriorly. Over this area tactile fremitus and voice sounds were exaggerated. Over the left upper chest, both anteriorly and posteriorly, the percussion note had a tympanitic quality, tactile fremitus was poorly transmitted and breath sounds were diminished. There were no audible wheezes such as were heard over the remainder of the chest. The heart was not enlarged. The rhythm was regular. There were no murmurs heard. The blood pressure was 104/60 mm. of mercury.

Laboratory Data. The red blood cell count was 4.97 millions; hemoglobin, 15 gm. and white blood cell count, 9900. The electrocardiogram was normal. The blood Wassermann reaction was negative. The roentgenogram of the chest (Fig. 7) showed many calcified areas in the right lung from apex to the level of the sixth posterior rib. There were increased linear markings with rather coarse feathering in the right lung from the sixth posterior rib to the base. The left pulmonary field showed a large area of decreased density above the level of the seventh posterior rib. Fine interlacing lines traversed this area. There were increased linear markings with rather coarse feathering in the left lung from the seventh posterior rib to the base. The heart was shifted toward the right side.*

Clinical Diagnoses. Chronic bronchitis; bronchial asthma; obstructive pulmonary emphysema; emphysematous bullæ; chronic fibroid tuberculosis, right apex.

CASE 6.—J. D. (No. 69826) was a 38-year-old electro-plater who had no complaints referable to his cardio-respiratory system save for some limitation in exercise tolerance. The lesions in the lung were found when a roentgenogram of the chest was taken prior to a major abdominal operation. In the past he had a history of chorea at the age of 8 years, and pneumonia with pleurisy at 16 years. Since then he had had recurrent attacks of pleural pain without cough or fever.

Physical examination revealed a well developed and nourished man of 38, who did not appear ill. There was no respiratory distress, cyanosis or clubbing of the fingers. The thorax was symmetrical and expansion limited bilaterally. The percussion note was resonant throughout both lungs except at the right base where there was slight impairment. The left base descended farther than the right. The breath sounds over the left lung were normal. On the right anteriorly the breath sounds were suppressed and broncho-vesicular in quality. At the right base posteriorly the breath sounds were broncho-vesicular in type, accompanied by fine crackling râles. The heart was slightly enlarged to the left. There was no enlargement to the right. The first sound at the mitral area was accentuated followed by a short whiff. The pulmonic second sound was greater than the second aortic sound. There was a fairly loud early diastolic murmur heard just to the left of the sternum in the fourth and fifth interspaces. The blood pressure was 105/65 mm. of mercury.

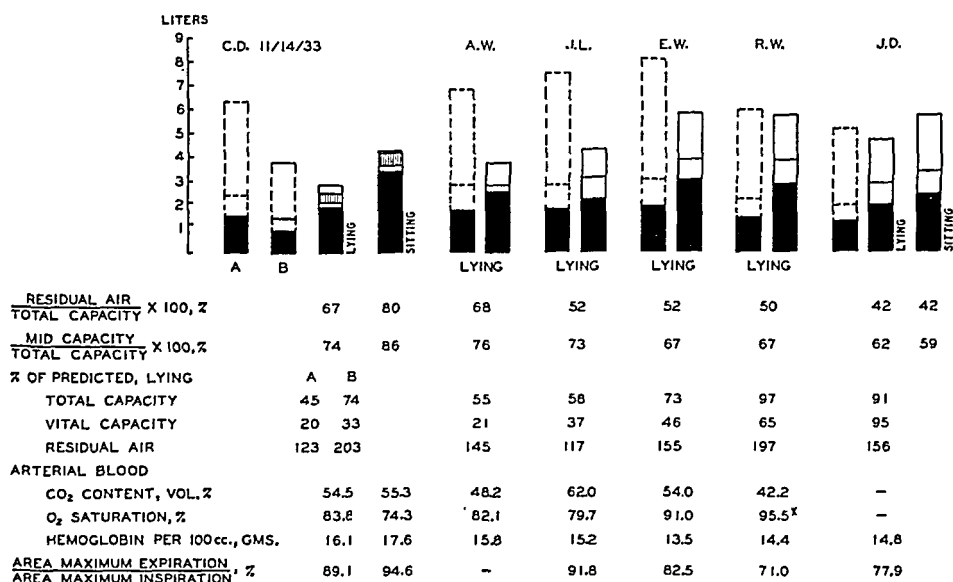
Laboratory Data. The red blood cell count was 4.19 millions; hemoglobin, 13 gm. and white blood cell count 7700. The blood Wassermann test was negative. The electrocardiogram showed left axis deviation. Roentgenogram of the chest (Fig. 8) showed an area of lessened density in the right lung extending from the fifth posterior interspace to the eighth. This

* This patient was kindly referred to us by Dr. Jacob D. Goldstein.

area was about 8 cm. in diameter and suggested a localized area of emphysema. In the lower portion of the lung there were areas of infiltration from the level of the ninth posterior rib to the base. There were increased linear markings in the lower half of the left lung. The costophrenic angles were slightly hazy. There was some enlargement of the heart in the region of the left ventricle. Four additional roentgenograms taken during a period of 2 years showed no change in these conditions, except the shadows in the right lower lung became more dense.

Clinical Diagnoses. Emphysematous bullæ; rheumatic heart disease with aortic insufficiency.

Methods. The methods employed in this investigation have been amply described in previous communications from this clinic.^{5,7,11,12}



* HYPERVENTILATED

FIG. 9.—The pulmonary capacity in cases of emphysematous bullæ and congenital cystic disease of the lungs. Each case is represented by two columns, the left-hand column designates the predicted value while the right one the observed value. The black area represents the residual air while the white space above the vital capacity. "A" under C. D. represents the values when they are predicted from the total area of the chest, including the area of the cysts, while "B," the values when the area of the cysts is not included in the prediction.

Results. Details of the measurements of the pulmonary capacity are given in Figure 9 and Table 1. None of the patients were having paroxysms of bronchial asthma at the time the pulmonary capacity was determined. In 4 instances (C. D., A. W., J. L., E. W.) there was a marked reduction in the total capacity while in the remaining cases this capacity approximated the predicted one. The vital capacity was reduced to an abnormally low level in all instances except one (J. D.) who complained of dyspnea only on moderate to severe exertion. The residual air was increased in all cases, but the increment was not nearly so marked as one would expect in the

presence of such large air-filled cavities. Due to the marked decrease in the vital capacity and the moderate increase in the residual, the latter volume constituted an abnormally high percentage of the total capacity. The values for the ratio $\frac{\text{mid capacity}}{\text{total capacity}} \times 100$ were definitely elevated, in all but 1 case (J. D.). Likewise the tidal volume constituted a much higher percentage of the vital capacity than normally.

TABLE 1.—CARDIORESPIRATORY OBSERVATIONS ON A PATIENT WITH LARGE BILATERAL PULMONARY CYSTS.

Case C. D. No. 52358.	Nov. 14, 1933.		Nov. 15, 1933. Lying.	Nov. 18, 1933. Lying.	Nov. 24, 1933. Lying.
	Lying.	Sitting.			
Total capacity, liters	2.83	4.26	2.46	2.55	3.17
Vital capacity, liter	0.94	0.86	0.76	0.84	0.98
Mid capacity, liters	2.09	3.66	1.86	1.89	2.35
Complementary air, liter	0.74	0.60	0.60	0.66	0.82
Reserve air, liter	0.20	0.26	0.16	0.18	0.16
Residual air, liters	1.89	3.40	1.70	1.71	2.19
Ratios:					
Residual air/Total capacity $\times 100$, %	66.8	79.8	69.1	67.1	69.1
Mid capacity/Total capacity $\times 100$, %	73.9	86.0	75.6	74.1	74.1
Tidal volume/Vital capacity $\times 100$, %	43.6	62.8			
Oxygen consumption per min., cc. .	240.0	308.0			
Tidal air:					
Carbon dioxide, %	2.94	3.19			
Oxygen, %	17.11	17.00			
Nitrogen, %	79.95	79.81			
Ventilation per minute, liters . .	6.84	9.93			
Respiratory rate	17.0	20.0			
Tidal volume, cc.	410.0	540.0			
Alveolar air:					
Carbon dioxide, %	5.43	6.21			
Oxygen, %	13.52	12.48			
Nitrogen, %	81.05	81.31			
Venous pressure, mm. H ₂ O	100, left				100, left 85, right 20.5
Blood velocity, seconds	
Air removed from cysts:					
Carbon dioxide, %	8.36	7.65	
Oxygen, %	7.61	7.79	
Hematocrit, %	48.7				
Red blood cells, millions	6.41				
Hemoglobin, gm.	16.88				
Viscosity	5.8				

The alterations in the pulmonary capacity are strikingly accentuated on assuming the sitting position (Fig. 9, C. D.). The total capacity and residual air were markedly increased and the patient utilized 62.8% of his vital capacity during each respiration. Accompanying these changes in the volume of the lungs, the oxygen consumption per minute and the respiratory rate were augmented.

Likewise there was an increase in the carbon dioxide percentages of the expired and alveolar air. Change of posture affected several other measurements. In the supine position the excursions of the diaphragm were normal in type, while in the upright position they moved paradoxically, *i. e.*, during inspiration they ascended and *vice versa*. The oxygen saturation of the arterial blood decreased from 84% in the lying to 74 in the sitting posture. Likewise the expansion of the chest was markedly diminished in the upright position. Although the alveolar ventilation was greatly impaired in the lying position, while sitting the abnormalities were greatly intensified and dyspnea was more acute.

Roentgenographic Measurements. The size of the chest was larger in this group of cases (18.1 to 23.8 liters) than that of normal men of the same age group (average 15 liters). The shape of the chest was definitely altered. The anteroposterior diameter was greater than normal, thereby increasing the ratio $\frac{\text{depth}}{\text{width}} \times 100$. Likewise the height of the pulmonary fields more closely approximated their width (Table 2). The ability to expand the chest was greatly diminished in all instances, as indicated by the excursions of the diaphragms, lateral movement of the chest, rib rotation and the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$ (Table 2).

TABLE 2.—ROENTGENOGRAPHIC MEASUREMENTS.

	Normal (av. values).	C. D.		A. W. Lying.	J. L. Lying.	E. W. Lying.	R. W. Lying.	J. W. Lying.
		Lying.	Sitting.					
Excursion of diaphragm, cm.:								
Right	6.0	1.6	P	..	0.5	2.6	5.8	4.3
Left	6.0	1.5	P	..	0.7	3.2	5.0	5.1
Transverse expansion of chest, cm. .	2.9	1.1	1.3	..	1.0	1.9	2.8	2.3
Area of pulmonary fields, cm.: ²								
Maximum inspiration	824.0	886.0	939.0	899.0	915.0	769.0	629.0
Maximum expiration	734.0	838.0	..	825.0	755.0	547.0	490.0
Ratio:								
Area maximum expiration Area maximum inspiration $\times 100$, %	65.0	89.1	94.6	..	91.8	825.0	71.1	77.9
Rib movement, degrees	19.0	11.0	19.0	11.0	16.0	20.0
Radiological chest value, liters . .	15.0	..	18.1	22.1	22.0	23.8	16.9	15.1
Inspiration								
Depth Width $\times 100$, %	73.0	82.7	82.7	80.3	75.9	75.4
Height* Width† $\times 100$, %	69.0	97.5	103.0	99.3	84.2	77.1

P = paradoxical movement of diaphragm.

* Average height both pulmonary fields at expiration.

† From roentgenogram, expiration.

Analyses of the gaseous content of the arterial blood are shown in Figure 9. The values for the carbon dioxide content were high normal in 3 cases (C. D., J. L., E. W.) while in the remainder there was no deviation from the normal. On comparing oxygen content

and capacity of the arterial blood a low saturation was found in 4 instances. There was no evidence of polycythemia found even in the presence of low arterial saturation. Here again is found a reasonably close correlation between the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ and the saturation of the arterial blood with oxygen. When the value for this ratio was over 45%, a low value for the oxygen saturation of the arterial blood was found in all but one instance. In this instance the individual, R. W., was observed to hyperventilate his lungs.

In 1 instance, the subject (E. W.) performed 300 kg. per minute for 5 minutes of work on a stationary bicycle ergometer. During this performance he complained of slight breathlessness. The value for the expression $\frac{\text{total ventilation}}{\text{vital capacity}}$ was 61, one slightly above the level of dyspnea previously found for normal individuals, *viz.* 51. Likewise while performing this amount of work the minute ventilation during the final 2 minutes of exercise constituted 88% of his maximum ventilatory power in contrast to the normal average value of 35%. His pulmonary reserve was greatly reduced, *viz.* 29 liters compared with 63 liters for normal individuals.

Discussion. The functional changes referable to the respiratory system in this series of cases are similar to those observed in patients with obstructive pulmonary emphysema.^{1,8,10} The most common symptoms were productive cough and dyspnea. The volume of the chest was large and its expansion greatly diminished. The antero-posterior diameter of the chest was increased and the thorax was held at an inspiratory position. The vital capacity was greatly reduced in all instances except 1 (J. D.). The remaining components of the total capacity are at variance with the typical picture seen in cases of obstructive emphysema, in which the total capacity approximates the predicted values and the residual air is greatly increased as is the case in emphysema, while in the cases with cystic lungs the residual air was only slightly increased. The total capacity was markedly reduced. The reduction in the total capacity is probably due to the fact that the accuracy of determining the residual air by the oxygen dilution method is somewhat impaired in the presence of such bizarre changes in the lungs. The mixing between spirometer and lungs is probably not homogeneous at the end of the rebreathing period.² It is conceivable that in many of these cases, especially in the instance of C. D., the residual volume does not include the contents of the cysts because of poor ventilation between the tidal air and the gaseous content of the cysts. Pulmonary cysts with gaseous contents are always in communication with the outside air, for, if this were not so, the air would soon be absorbed and the walls collapse. There are several reasons for believing that the ventilation in such cysts is poor. In the case of C. D., at autopsy there was found no large bronchial communica-

tion with the cysts. Due to compression of the adjacent pulmonary tissue the communications were probably small and tortuous. The tension of the carbon dioxide and oxygen of the gas aspirated from the cysts was very similar to that that one would expect of the mixed venous blood of the patient, indicating that the gaseous exchange between the cyst and outside air was minimal. After forcefully rebreathing for 23 seconds a mixture of gas containing 15% acetylene, the gas removed from the cavity of the right lung showed an acetylene percentage of only 0.15. Fluoroscopic examination showed no change in the size of the cavities during respiration. Likewise no change in the area of the cavities, between maximum inspiration and expiration could be found on a doubly exposed roentgenogram when measured by means of an accurate planimeter. One would suppose then that during the rebreathing period the contents of the cavity was not measured. If the volume of the cysts were included in the volume of the air remaining in the thorax at the end of maximum expiration, the residual air should be very much increased, resulting in a normal or high volume for the total capacity. The factors responsible for the marked alterations in the pulmonary capacity and for the arterial anoxemia have been described elsewhere and need not be stressed here.^{1,7,8,10}

A point of interest in the case of C. D. was the observation that the patient was worse when he was in the sitting position than when he lay flat. The increased respiratory distress on assuming the upright position may readily be explained on a mechanical basis. In contradiction to normal individuals the vital capacity decreased on assuming the upright posture, resulting in an increase in the ratio $\frac{\text{tidal volume}}{\text{vital capacity}} \times 100$. Consequently, the pulmonary reserve was reduced and each inspiration required greater effort to effect an adequate tidal volume in the sitting as compared with the recumbent posture. The factor responsible for the diminution in the vital capacity was probably the paradoxical movements of the diaphragm. On changing from the lying to the sitting position the pressure within the cyst became more positive. This decrease in the vital capacity with change in posture has been noted in about half of the cases with marked obstructive emphysema that we have investigated. By assuming the upright posture the alveolar ventilation was further impaired as evidenced by the increase in the carbon dioxide content of the arterial blood and the increased anoxemia. A similar case was reported by Means¹⁵ in his monograph on "Dyspnoea." The patient had severe dyspnea without orthopnea. At autopsy, he was found to have a lymphoma of the mediastinum. The author believed that the major portion of the dyspnea was mechanically produced.

In Table 3 the cases are arranged according to their disability as rated by interrogating the patients. There was a fairly close corre-

lation between the ease with which shortness of breath was produced and the various components of the pulmonary capacity, anoxemia and expansion of the chest. It is of interest to note that the lesions seen on the roentgenogram of case J. D. are similar to, although less extensive than those of C. D. The former patient had little or no disability while the latter was dyspneic at rest. This supports our contention that the roentgenographic lesions do not always parallel respiratory function and that functional tests are necessary in many instances to properly evaluate disability.

TABLE 3.—RELATIONSHIP OF DYSPNEA TO CERTAIN RESPIRATORY MEASUREMENTS.

Case.	Dyspnea.*	Vital capacity, % of predicted.	Residual air Total capacity × 100.	Mid capacity Total capacity × 100.	Tidal volume Vital capacity × 100.	Oxygen saturation, arterial blood.	Area max. expiration × 100. Area max. inspiration	Depth Width × 100.
J. D. . . .	+	95	42	62	15	..	78	75
R. W. . . .	++	65	50	67	25	95.5	71	76
E. W. . . .	++	46	52	67	28	91.0	83	80
J. L. . . .	++	37	52	73	27	79.7	92	83
A. W. . . .	+++	21	68	76	47	82.1		
C. D. . . .	++++	20	67	74	44	83.8	89	83

* ++++ = at rest; +++ = on slight exertion; ++ = on moderate exertion; + = on severe exertion.

Dyspnea in individuals with congenital cystic disease of the lung and emphysematous bullæ may be readily explained by mechanical impairment of the respiratory bellows. In other words, the lungs are unable to supply an adequate amount of oxygen to the tissues. In 1 case (C. D.), in order to meet the demands of the body at rest, respiratory effort was close to the maximum and dyspnea was so severe that muscular exertion was impossible. In several of the other cases (A. W., J. L., and E. W.) the ventilatory reserve was greatly reduced consequently slight increase in the demand of the body for oxygen caused dyspnea.

The nature of the pulmonary cysts in these cases demands a brief discussion. Cystic disease of the lung is usually classified under two main groups, the congenital and the acquired forms.³ Under both headings one may find the lesions to be either unilateral or bilateral and solitary or multiple. Either may contain fluid or air. When round shadows are found in the roentgenogram of the chest, a whole host of conditions creeps into the differential diagnosis. The many possibilities have been recently enumerated and discussed by various observers and need not be stressed here.^{4,17,19,21 et al.}

The question that arises from the study of this group of adults is, Are these air-filled cysts congenital in nature and develop later in life to produce symptoms or are they the result of acquired chronic changes in the bronchial tree and pulmonary parenchyma? The patients in this series had certain things in common; (a) all had a history of respiratory infection, (b) all but 1 (J. D.) had symptoms of respiratory insufficiency, (c) in all instances there was pulmonary emphysema, fibrosis or both, and (d) half the patients had paroxysms of bronchial asthma. It is particularly difficult from a clinical standpoint to understand just what part chronic pulmonary infections play in this picture. It is well known that bullæ producing round shadows on the roentgenogram may be the result of marked emphysematous changes in the lungs. Several authors^{9,13,16,20} have reported such cases. On the other hand, proven cases of congenital cystic disease have been found in very old individuals, who had no symptoms referable to these changes throughout their whole life. Likewise congenital defects may remain silent until later in life when some pulmonary infection or disorder is superimposed.

In the first patient (C. D.), who presented the large bilateral cysts, so-called balloon cysts, there was a great deal of discussion concerning the nature of the cysts even after careful pathologic examination. The following anatomic facts appear to support the proportion that in this case the lesions were acquired; pigmentation of the compressed alveoli composing the wall of the cyst and the numerous large emphysematous bullæ in the peripheral portions of the lower lobes. Many of these smaller bullæ had the same anatomic configuration that the larger cysts had. In addition, this patient was exposed to a considerable amount of dust over a long period of years. It is not uncommon to find a certain amount of fibrosis, bronchial infection and varying degrees of emphysema in men who worked in the mines for a great many years. Prior to this patient's army life there was no history of disability. The history of gradually increasing disability indicates that the process was gradually progressing and that the cysts were increasing in size over a period of years. One would expect then that the bronchial communications had a valve-like action, a one-way mechanism at the orifices. However, on the other hand, one may argue that the patient had the defect since birth and that the various superimposed factors (dust and bronchial infection) simply produced the valve-like action in the bronchial tree, causing the cysts to increase in size and other portions of the lung to be compressed.¹⁸ In either case, the end result may be the same. This case is very similar to those reported by Wilson,²⁰ Karan and Haymaker¹³ and Jacobaeus.⁹ These authors concluded that the cysts were not congenital but developed during life from changes in the bronchial tree.

Although the symptoms and signs of respiratory insufficiency are lacking in the sixth case (J. D.), from a roentgenographic viewpoint

it is very similar to that of the first patient (C. D.). The process is unilateral and much less advanced, but the roentgenograms have similar characteristics. Post-pneumonic alterations of the lung may have been the original disease process, leading to breakdown of the alveoli, resulting in compression of the lower and middle lobes by the expanding emphysematous bullæ in the upper lobe. The ill defined wall and the scattered lacy network throughout the cysts suggest a cavity formed by breakdown of the pulmonary parenchyma rather than congenitally formed cysts.

The third patient (J. L.) had paroxysms of bronchial asthma for 14 years. The roentgenograms as well as measurements of the residual air indicate that he had well marked obstructive pulmonary emphysema. It seems reasonable to assume that the areas of decreased density as seen on the roentgenogram of the chest, is due to breakdown of the alveoli from bronchial obstruction and may be classified as emphysematous bullæ rather than congenital cystic disease of the lung. The fifth patient (Fig. 7) shows similar changes in the left upper lobe. The history of asthma, however, was of only 3 years' duration. In the fourth case (R. W.) the history of bronchial infection, bronchial asthma and exposure to dust containing some silica over a period of years and the ill defined outline of the area of increased radiability of the lungs are sufficient evidence to make the diagnosis of obstructive emphysema and emphysematous bullæ.

The second patient (A. W., Figs. 5 and 6) has multiple cysts and on the roentgenogram the cavities are irregularly arranged, are spherical, have sharply defined outlines, with little evidence of pulmonary infiltration between the walls of the cysts. These characteristics are considered by many to be the criteria for congenital cystic disease of the lung.

It appears then from a clinical viewpoint it is often impossible to distinguish between congenital cystic disease of the lung and emphysematous bullæ. The multiple cysts which are more commonly found in adults as a rule cause no marked disability unless there is a superimposed infection and are usually discovered accidentally later in life. When annular cavities with poorly defined walls, which show no pulmonary markings but fine linear strands traversing the cystic space associated with respiratory disability and pulmonary emphysema or fibrosis, emphysematous bullæ should always be included in the differential diagnosis.

Summary and Conclusions. Six patients with air-filled pulmonary cavities were investigated from a functional viewpoint. In all cases the pulmonary capacity was determined, roentgenographic measurements were made and the arterial blood was analyzed for its oxygen and carbon dioxide content. In 1 case the ventilatory response during exercise was determined. One patient (C. D.) with large bilateral pulmonary cavities came to necropsy and the

pathologic lesions are described. From the aforementioned studies the following conclusions may be drawn:

1. In half of the cases the total capacity, as well as the vital capacity, is reduced while the residual air is only slightly increased. Evidence has been produced which indicates that in these 4 cases the volume of the cysts is not included in the residual air. This accounts for the small increase in the residual air and the marked decrease in the total capacity. In the remaining cases the alterations in the pulmonary capacity are typical of those of obstructive pulmonary emphysema, *i. e.*, a marked decrease in the vital capacity with a corresponding increase in the residual air, resulting in a normal value for the total capacity.

2. The ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ is increased in all cases.

3. The volume of the chest is larger in this series of cases than in a group of normal men of the same age group. The shape of the chest is characteristic of obstructive emphysema, *i. e.*, barrel-shaped. The ability to expand the chest in all cases is markedly diminished.

4. There is a slight retention of carbon dioxide in 3 cases, as evidenced by the carbon dioxide content of the arterial blood. There is a certain degree of anoxemia in 4 of the cases. There is a reasonable close correlation between the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ and the oxygen saturation of the arterial blood.

5. The pulmonary reserve is reduced in cases of emphysematous bullæ and congenital cystic disease of the lung.

6. The degree of dyspnea is closely related to the decrease in vital capacity and expansion of the chest and to the increase in the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$.

7. Dyspnea in such cases may be readily explained by the mechanical impairment of the respiratory bellows.

8. The nature of the pulmonary air cysts in this series has been discussed.

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THE EFFECTS OF LARGE DOSES OF INSULIN ON BLOOD HYDRATION IN MAN.*

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THE use of insulin in the treatment of schizophrenia affords good opportunity for the study of phenomena associated with hypoglycemia produced by insulin in relatively healthy men and women. Clinical observation suggests that marked losses of water and electrolytes occur through sweating and hyperventilation when hypoglycemia is allowed to persist for several hours. Work with animals, while there has been some disagreement,⁵ in general supports the results of Drabkin and Edwards³ and Drabkin² who reported that insulin in amounts of 20 units per kg. of body weight brings about profound hemoconcentration in dogs. Chaikelis,¹ using doses up to 1 unit per kg. in rabbits, found moderate anhydremia, as shown by increases in plasma solids and in red cell count and hemoglobin; he attributes the last two findings to splenic contraction. A review of the literature to 1934 appears in Chaikelis' article. More recently, Drabkin and Ravdin⁴ have reported that anhydremia is a factor in the cycle of events leading to convulsions in severe hypoglycemia produced by insulin in dogs.

Since data on man are, so far as we know, incomplete, and the quantity of insulin necessary to produce coma in man is far below the dose used by Drabkin in dogs, it was felt that the effects produced by less abnormal quantities of insulin in man might be of interest. A study of blood hydration in artificially produced insulin hypoglycemia was therefore undertaken.

Methods. The subjects of this study were 12 patients at the Philadelphia General Hospital.† Of these, 10 were diagnosed as schizophrenics, 2 as manic-depressives. Prior to acceptance for the insulin treatment, electrocardiograms, urea clearances and basal metabolic rates (on cooperative patients) were obtained. These studies, repeated at intervals, insured that the subjects in this series, men and women in the first third of life, were in reasonably good physical health.

Fifteen experiments on 12 patients (8 men and 4 women) and 2 control experiments on 2 men are reported. The following procedure was used. Insulin, in a dose found previously to produce coma in the subject studied, was given subcutaneously between 7 and 8 A.M. Coma usually developed 2 to 3 hours after injection and was terminated 1 to 2 hours after onset by intravenous injection of 50 or 100 cc. of 33% glucose. Food was withheld from the patient for 10 hours before the insulin injection; no food or fluid was given during the experimental period. No restriction of food or fluid

* Awarded the annual Charles W. Burr Prize by the Medical Board of the Philadelphia General Hospital.

† Drs. Burr, Hadden and Strecker were kind enough to allow these observations to be made on patients on their services.

after termination could be enforced under the circumstances. Blood samples were drawn at intervals during the coma and after termination, and compared with a fasting sample taken just before insulin was given. At least 5 samples were secured in each experiment.

Hemoglobin, red cell volume and refractive index of the plasma were determined in duplicate or triplicate. Venous blood was drawn as uniformly and rapidly as possible into a dry syringe and 4 cc. mixed with 8 mg. of dry sodium oxalate in a small test-tube. Precautions were taken to avoid hemolysis by gentle handling, and evaporation by keeping the rubber-corked tubes in a moist chamber between manipulations. The tubes were inverted 20 to 30 times to ensure thorough mixing. Hematocrit values were determined in Wintrobe tubes after centrifuging all samples in a single experiment together for 30 minutes at 2200 r.p.m. (centrifuge radius 15 cm.). Since the same concentration of sodium oxalate was used in all samples, its effect on cell volume would not influence comparison between them. A dipping refractometer was used for the refractive indexes, all readings being made at a temperature of 19° C. Hemoglobin was determined by diluting 0.5 cc. of blood to 50 cc. with N/10 HCl in a volumetric flask; after standing 24 hours, the acid hematin solutions were compared colorimetrically, using the fasting blood hematin solution as a standard. One or more blood sugar determinations (modified Folin and Wu method) were done in each experiment.*

All patients were weighed before being given insulin and shortly after termination of the coma.

The dosage of insulin varied from 0.75 to 3.24 units per kg. of body weight. The smallest amount given was 43 units, the largest 245 units.

Results. Eight of the 12 patients showed marked sweating during coma, 4 remained relatively "dry." This difference in response has been previously noted by Sakel⁷ and thought to have prognostic significance. The blood sugar levels in all subjects shortly before termination ranged between 15 and 30 mg. %. No relationship was found between the weight or other characteristics of the patient and the dose necessary to produce coma.

Refractive indexes of the plasma were secured in all 15 experiments, hematocrit determinations in 14 and hemoglobin values in 6. The results are summarized in Table 1.

TABLE 1.—CHANGES IN THE BLOOD OF SUBJECTS IN THE THIRD TO FOURTH HOURS OF INSULIN HYPOGLYCEMIA.

Determination.	Number of experiments.	Number showing increase.	Range of increase.	Number showing decrease.	Range of decrease, %	Number showing no change.
Red cell volume . . .	14	10	4-12%	2	5	2
Hemoglobin	6	5	7.8-9.3%	0	0	1
Refractive index of plasma	15	12	0.00037-0.00256	0	0	3

The majority of subjects, as seen in Table 1, showed after 3 to 4 hours of insulin hypoglycemia a moderate increase in red cell volume and hemoglobin. This result might be produced by an increase in circulating cells following splenic contraction, as was concluded by Chaikelis¹ to be the case in rabbits after the injection

* Miss E. Fortunato kindly performed the blood sugar determinations.

of insulin. In our material, however, the rise in hemoglobin and red cell volume was accompanied by increase in plasma refractive index, allowing us to consider loss of water from the blood to be the basis of the changes found.

TABLE 2.—SUMMARY OF MAXIMUM CHANGES IN 3 TO 4 HOURS OF INSULIN HYPOGLYCEMIA.

1	2	3	4	5	6	7	8	9	10	11
No.	Name and sex.	Date, 1937.	Air temperature, °C.	Amount of insulin in units.	Amount of insulin, units per kg.	Weight loss in %.	N_D fasting and highest values 1.3—.	Maximum changes before termination in % of fasting value.		
								Plasma protein.*	Hematocrit.	Hemoglobin.
1	J. D. M	Oct. 14	22.5	43	0.75	1.2	4947 4966	2.2†	1.9†	7.8†
2	M. S. F	Aug. 24	22.5	55	1.19	2.9	4895 4966	6.2†	3.3†	
3	J. L. M	Sept. 8	..	100	1.28	4.5	4973 5047	5.4	4.2	
4	J. L. (1)	Sept. 4	28.0	100	1.33	3.3	4862 5068	16.0	7.0	
5	J. L. (2)	Oct. 6	27.6	110	1.39	..	4940 5105	12.4	5.2	8.3
6	C. R. M	Aug. 17	28.0	90	1.61	3.9	4869 5036	12.9	12.0	
7	G. N. M	Oct. 22	23.7	120	1.62	2.4	4823 4947	10.4	0	0
8	M. C. (1) M	Sept. 15	19.5	142	1.66	0†	5031 5068	2.6	4.0	
9	A. Z. F	Aug. 30	28.0	95	1.74	0.5†	4903 4954	3.8	4.2	
10	E. H. F	Sept. 2	28.0	105	1.85	1.6	4851 4851	0	1.5	
11	J. N. M	Aug. 13	..	180	2.30	Profuse sweat	4761 5017	22.0	6.7	
12	M. K. F	Oct. 16	22.0	100	2.49	0†	4862 4951	7.1	5.0	8.7
13	C. M. M	Sept. 21	22.0	150	2.53	1.15	4940 5162	16.5	8.0	8.5
14	M. C. (2)	Oct. 25	22.0	245	2.56	0.7†	4906 5095	14.5	7.2	9.3
15	A. B. M	Aug. 20	32.0	190	3.24	Profuse sweat	4951 5125	12.75		

* Calculated from change in refractive index. See text.

† Decrease to fasting or below fasting level before termination.

‡ "Dry shock."

When maximum figures in individual experiments (presented in some detail in Table 2) are compared, it is noted that the refractive index (N_D) changes fall into two groups. In one (Cases 3, 6, 8, 9 and 12) the increase in N_D , when translated into terms of plasma

protein concentration,⁶ corresponds fairly closely to the change in red cell volume and hemoglobin. Thus, for example, in Experiment 12, N_D rose from 1.34862 to 1.34951, corresponding to a change in plasma protein concentration of 7.1% from the fasting level. At the same time, the hemoglobin content increased by 8.7%. In the second group (Cases 4, 5, 11, 13, 14), figures derived from the refractive index show a water loss from the blood of 1.5 to 3 times the magnitude inferred from the hemoglobin and hematocrit values. Lack of direct plasma protein determinations does not allow us to rule out the possibility that in this set of experiments entrance into the plasma of material other than protein may have altered the refractive indexes over and above the increase produced by anhydremia. This reservation should be kept in mind when considering Column 9 in Table 2, which gives the protein values calculated from the refractive indexes. In any case, we feel that the similar direction of the results obtained indicates an increase in concentration of the blood through loss of water rather than addition of cells. To illustrate the first group of experiments, Figure 1 (Case 12) is appended; the other group is represented by Figure 2 (Case 13).

In the first 3 hours of the insulin effect, the increase in hemoglobin exceeded the increase in red cell volume (by 2 to 7% in 5 experiments), so that there was evidently loss of water from cells as well as from plasma with consequent shrinkage of erythrocytes. After 3 hours, the hematocrit values rose more rapidly to parallel, though not necessarily to reach, the hemoglobin levels (Figs. 1 and 2).

Four experiments presented some exceptions. In Cases 1 and 2, no stable change was produced probably because the quantities of insulin used were quite small, 0.75 and 1.19 units per kg. respectively. In both cases there appeared a transitory small increase in red cell volume and refractive index in the first 3 hours, followed by a fall within the next hour. A parallel increase in hemoglobin, greater than the change in red cell volume, was noted in Case 1.

One patient (Case 7) showed no appreciable change in hemoglobin or red cell volume in 4 hours when 1.62 units per kg. were administered; however, his plasma refractive index increased from 1.34823 to 1.34947 in the same time. Another subject (Case 10), a woman, given 1.85 units per kg., showed no significant change in red cell volume or refractive index within 4 hours. These patients differed from the others in that they presented manic-depressive rather than schizophrenic symptoms.

Weight losses, ranging from 0 to 4.5% of the body weight, were observed following the injection of insulin. The greatest losses were noted in the experiments conducted during the summer, when the sweating reaction produced by insulin in most of the patients was intensified by the high air temperature (28° to 32° C.) and humidity. It will be noted, however, in Table 2, that insulin pro-

duced concentration changes independently of air temperature. Furthermore, weight loss was not invariably associated with the effect of insulin. Thus the 4 patients (Cases 8, 9, 12, 14) who exhibited a "dry" reaction, lost little or no weight. Two of them (Cases 12 and 14), given about 2.5 units per kg. at 22° C., showed increases in hemoglobin of about 9% and in refractive index of 0.00087 and 0.00189 respectively; the other 2, given 1.7 units per kg., showed slight change. The change in blood concentration may be

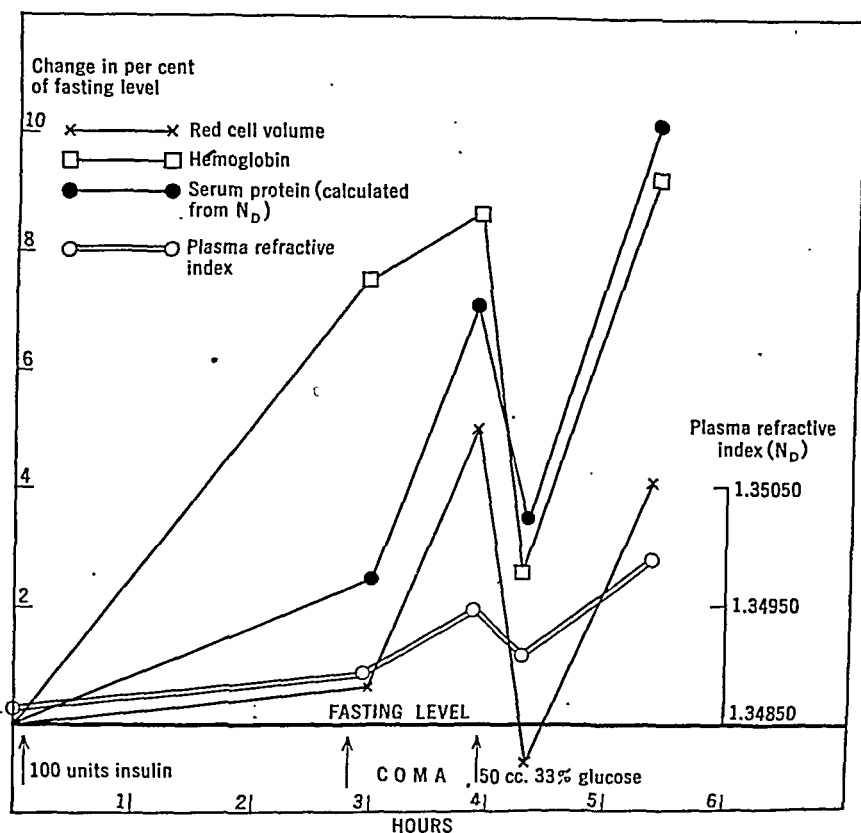


FIG. 1.—Experiment 12. Case M. K., white, female, aged 18 years. 100 units insulin (2.49 units per kg.). Air temperature, 22° C. "Dry shock," no weight loss. Graph illustrates experiment in which the increase in serum protein, calculated from change in refractive index, agrees fairly closely with the rise in hemoglobin.

due partly to loss of water through excessive sweating in some cases; in others, diuresis, actually observed repeatedly in 2 patients after the administration of insulin, or shifts of water within the body, or a combination of all these, may be responsible.

The phenomena involved are too complex to expect a constant relationship between the magnitude of insulin dose and the reaction produced; however, larger doses apparently produce greater effects. A stable change was not effected with doses below 1.3 units per kg.

(Experiments 1 and 2), while above 2 units per kg. maximum increases were obtained. Subject M. C., refractory to insulin, exhibited more marked changes at 2.56 units per kg. (Case 14) than he did at 1.66 units per kg., a dose insufficient to produce profound coma in his case. The variability of response to nearly the same amount of insulin by the same patient is illustrated by Subject J. L. (Cases 3, 4, 5).

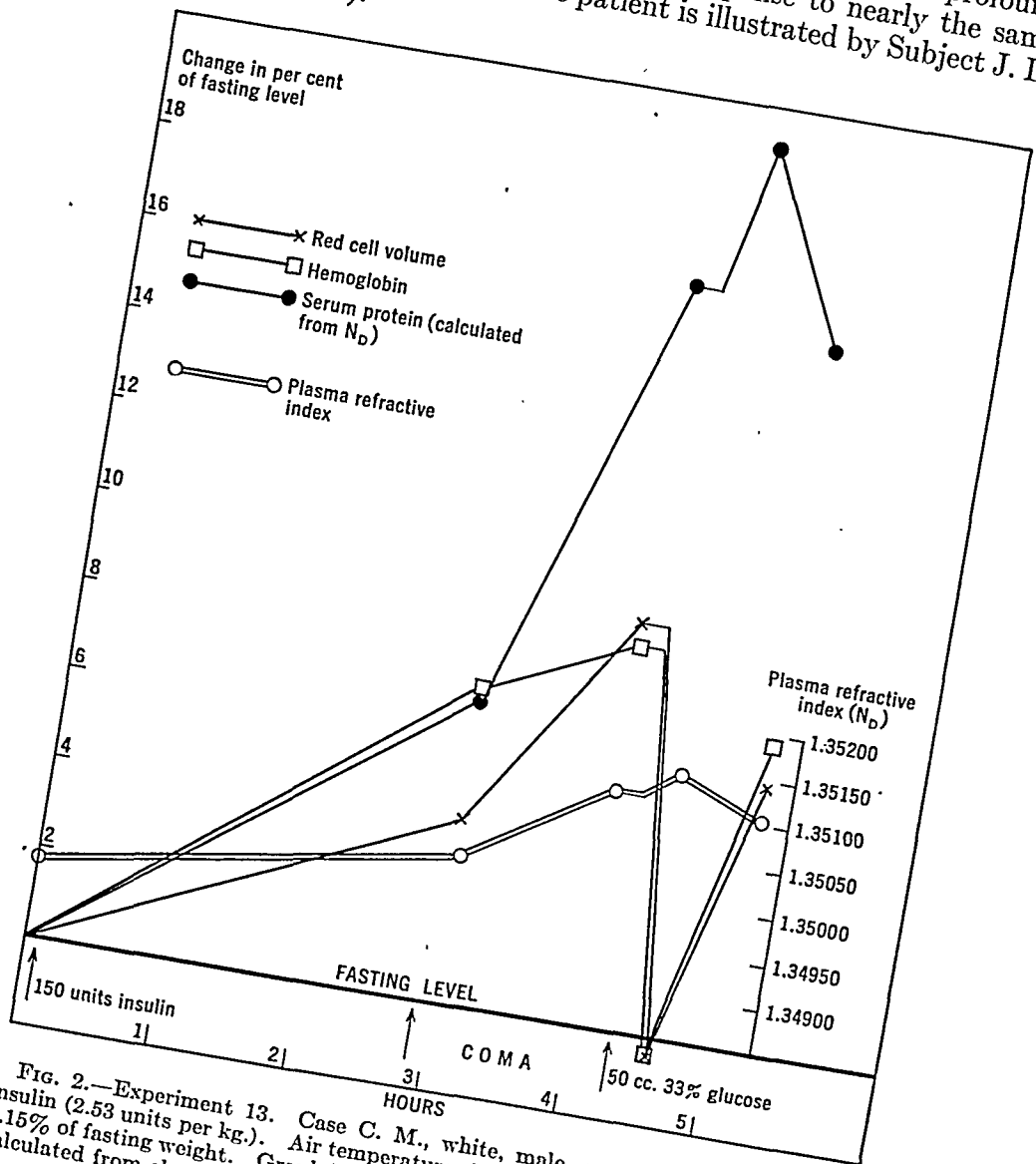


FIG. 2.—Experiment 13. Case C. M., white, male, aged 33 years. 150 units insulin (2.53 units per kg.). Air temperature, 22° C. Profuse sweating, weight loss 1.15% of fasting weight. Graph illustrates case in which the serum protein increase, calculated from change in refractive index, exceeds the rise in hemoglobin.

Changes After Termination. One or more samples of blood were taken at varying times after termination of coma by 50 or 100 cc. of 33% glucose intravenously, in 12 experiments on 10 subjects.

Fifteen to 40 minutes after termination, 6 of 7 samples showed a fall in hemoglobin and hematocrit red cell volume from the pre-termination values ranging from 1 to 8% of the fasting levels. In Experiment 1, a sample taken 28 minutes after termination showed an increase of 16.9% in red cell volume and 13.3% in hemoglobin; the plasma refractive index increased by 0.00251, a proportionate rise. This patient received the smallest dose of insulin (0.75 unit per kg.), but otherwise did not appear to differ from the others.

Five samples taken 1 hour or later after termination showed no change or only a slight increase from the pre-termination level in hematocrit or hemoglobin values. One such sample showed a further decline from an earlier post-termination fall and another an increase of 7.3% in red cell volume in terms of fasting level 1 hour after termination. In 5 out of 7 samples taken in the first hour after termination, the refractive index of the plasma showed a fall ranging from 0.00041 to 0.00126 below the pre-termination value; and in 6 out of 7 samples taken in the second hour, no change or an increase from the pre-termination value occurred.

Inspection of these figures shows that, usually, the hematocrit, hemoglobin and plasma refractive index values tend to fall, occasionally to the fasting level or below it, after termination with intravenous hypertonic glucose, and then rise again to their coma values during the next hour (see figures).

Controls. Changes not exceeding 2% in either direction in red cell volume and hemoglobin were observed in 2 fasting subjects kept in bed for 4 hours at 22° C. under conditions reproducing those in the insulin experiments. The greatest change in refractive index of the plasma observed was a fall of 0.00023 in 4 hours.

Comment. Judging by these results, changes in the water content of human blood under the influence of insulin are not as great as those observed in animals with the larger doses of insulin previously employed. The systemic disorganization noted in dogs³ did not occur in man when insulin in an amount just sufficient to induce coma was injected. It appears, however, that in the complex of reactions constituting the response to a large dose of insulin, a shift of water from the blood stream into the tissues occurs, an effect which may be manifested by the typical sweating reaction or by diuresis; and that both the shift of water and the sweating reaction may be absent without affecting the development of coma.

It should be noted that the changes reported are large enough to affect concentrations of electrolytes as well as non-electrolytes of the blood, so that concentration changes should be considered in studies of blood during insulin coma.

Summary. 1. The effect of insulin, administered in amounts sufficient to produce coma, upon the water content of the blood in 12 human subjects was studied.

2. Injection of 1.28 units per kg. of body weight or more caused

maximum increases above the pre-insulin values in erythrocyte volume of 4 to 12%; hemoglobin, 7 to 9%; plasma refractive index, 0.00037 to 0.00256, in 3 to 4 hours.

3. These changes were not always associated with marked sweating or loss of weight and cannot be entirely explained by external water loss, nor do they invariably accompany insulin hypoglycemia.

4. Attention is called to the importance of considering water concentration changes in studies of blood in insulin coma.

The author wishes to express his gratitude to Dr. S. DeW. Ludlum for the use of the laboratory in the Psychopathic Division at the Philadelphia General Hospital; to Dr. J. G. Reinhold for the suggestion responsible for this investigation and advice during its progress; and to Dr. H. Freed, in charge of the insulin treatment of the patients studied. The coöperation of Miss D. S. Grove, R.N., in the management of the patients is gratefully acknowledged.

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HYPERPARATHYROIDISM DUE TO PARATHYROID ADENOMA, WITH DEATH FROM PARATHORMONE INTOXICATION.

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SINCE Mandl's¹² demonstration in 1925 of the causative relationship between parathyroid tumors and osteitis fibrosa cystica, the clinical picture of hyperparathyroidism has been greatly augmented and clarified.¹ Several studies of acute parathormone poisoning of dogs are on record,^{2,3a,8} but no instance of death from parathormone poisoning in man has been observed clinically. It is the purpose of this communication to fill this gap in the natural history of hyperparathyroidism by recording an instance of death resulting from parathormone intoxication due to parathyroid adenoma.

Case History. A white housewife of 49 was admitted complaining of pain in the right chest and a feeling of tiredness. She had been admitted to another hospital on two occasions; first in 1926, with pyelitis, and the second time, in 1932, when a diagnosis of hydronephrosis on the right, with calcareous deposits in both kidneys, was registered. At this time blood chemical studies revealed the following: Ca, 12 mg. %; sugar, 100 mg. %; urea nitrogen, 30 mg. %; creatinine, 2 mg. %; and N.P.N., 50 mg. %. Phenolphthalein excretion: 35% in 1 hour with a total of 43% in 2 hours. The urine showed a few hyaline casts, many leukocytes, and a few red cells.

Roentgen ray pictures of the kidneys, taken in 1932, show the diffuse mottling of the parenchyma which is now regarded as characteristic of hyperparathyroidism.

From 1932 until May, 1936, she had been well, with a good appetite and doing her own housework. She then began to have dull pain under the right shoulder blade which persisted off and on until May, 1937, when she developed a pain in the anterior chest on the right, about the level of the third rib. During June, July and August, 1937, she became very weak, remaining in bed at one time for 2 weeks, and, despite an unfailingly good appetite, she constantly lost weight. During the past 12 months her weight has decreased 30 pounds. She has not been nervous, sleeps well, and has had no pain except in the right chest as described. No polydipsia or polyuria.

Physical examination on September 21, 1937, revealed a small, undernourished, white woman who did not appear at all ill, and who was pleasant, alert and coöperative. Temperature, 38.2° C.; pulse, 120; respirations, 22; blood pressure, 148/90. At the left lower pole of the thyroid there was a round, firm nodule, about 2 cm. in diameter. A rather indefinite mass was felt in the right hypochondrium which was thought to be the kidney. The physical examination was otherwise quite negative. The blood on admission was: erythrocytes, 3,500,000; hemoglobin, 10 gm. (66%); leukocytes, 6200; differential count not abnormal. The specific gravity of the catheterized urine was 1.012, with a trace of albumin and 10 W.B.C. per high-power field. No electrocardiographic study was made.

The correct diagnosis was not suspected until a Roentgen ray plate was made of the kidneys. Dr. Reeves reported: "The kidneys are quite low, and both are filled diffusely with a mottled deposit of calcium, typical of the changes seen in hyperparathyroidism (Fig. 1). All of the bones show generalized loss of calcium."

On the fourth day after admission, the blood chemical findings were as follows: Ca, 20 mg. %; phosphorus, 4.7 mg. %; and refractive index, 1.3492. The nodule at the left pole of the thyroid was now suspected of being a parathyroid tumor, and the patient agreed to an operation. She had been quite cheerful and uncomplaining, but during the next few days became rather depressed and complained a great deal of weakness and pain in the chest.

The blood chemical findings on the seventh admission day were: Ca, 22 mg. %; phosphorus, 4.8 mg. %; phosphatase, 23 Bodansky units; plasma N.P.N., 58 mg. %; total protein, 6.2 gm. %. A phenolphthalein excretion test on September 28 showed 20% excretion of the dye in 30 minutes and a total of 40% in 90 minutes.

Ten days after admission, it was noted that the patient was quite nervous, complained of feeling very weak, and was hoarse. The temperature was 38.5° C.; pulse, 120. The surgical consultant felt it advisable to postpone operation. The patient had had a slight fever daily up to 38° C., but on the last 2 days of life this had increased to 38.5° C. Throughout her stay the pulse was accelerated out of proportion to the fever. The last note on October 2 was as follows: "For the past 48 hours the patient has changed remarkably in her reactions. She has complained of great weakness and nervousness and, in contrast to her former cheerfulness, has been quite tearful. The rise in temperature of the past two days has been attributed to a possible upper respiratory infection. Tonight she complained of generalized aching pain. This morning at about 3 A.M. she called the nurse, who found her gasping for breath and quite cyanotic. Before I could reach the ward she had expired."

A complete *autopsy* was performed and the anatomic diagnosis was as follows: "Cystic and partly calcified and necrotic tumor of the parathyroid gland (lower left pole of thyroid). General intoxication (parathormone) with widespread injury necrosis and calcification of the connective tissue, especially that forming the basement membrane of the parenchymatous



FIG. 1.—The kidney pelves are filled with radio-opaque fluid. The calyces are seen to enclose the papillae, which are outlined by delicately mottled calcium deposits.

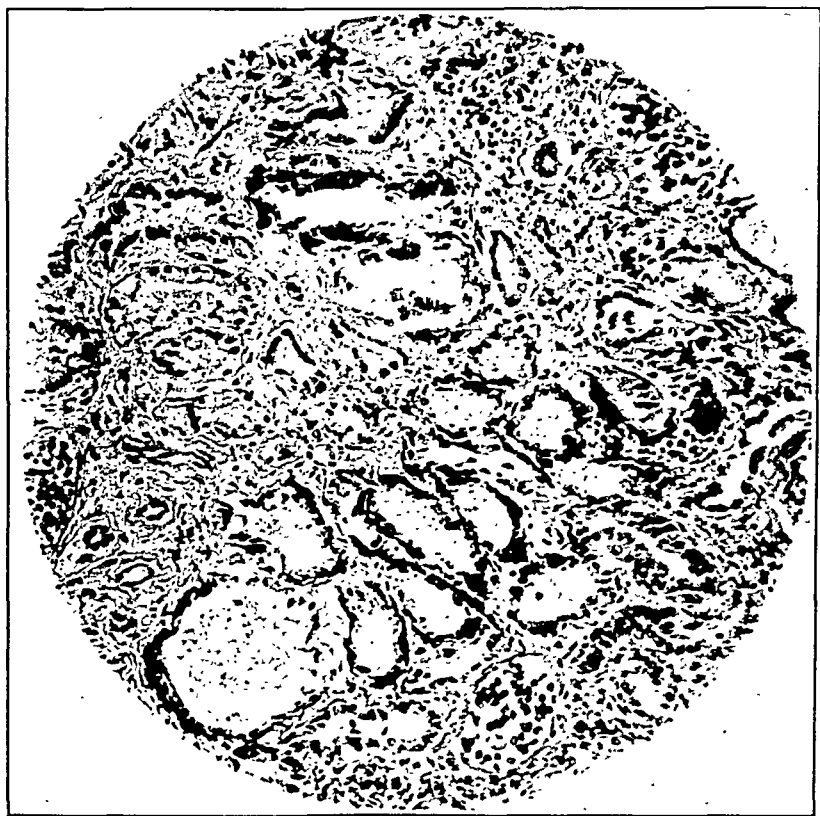


FIG. 2.—Calcification of basement membranes of kidney tubules, with necrosis of epithelial cells.

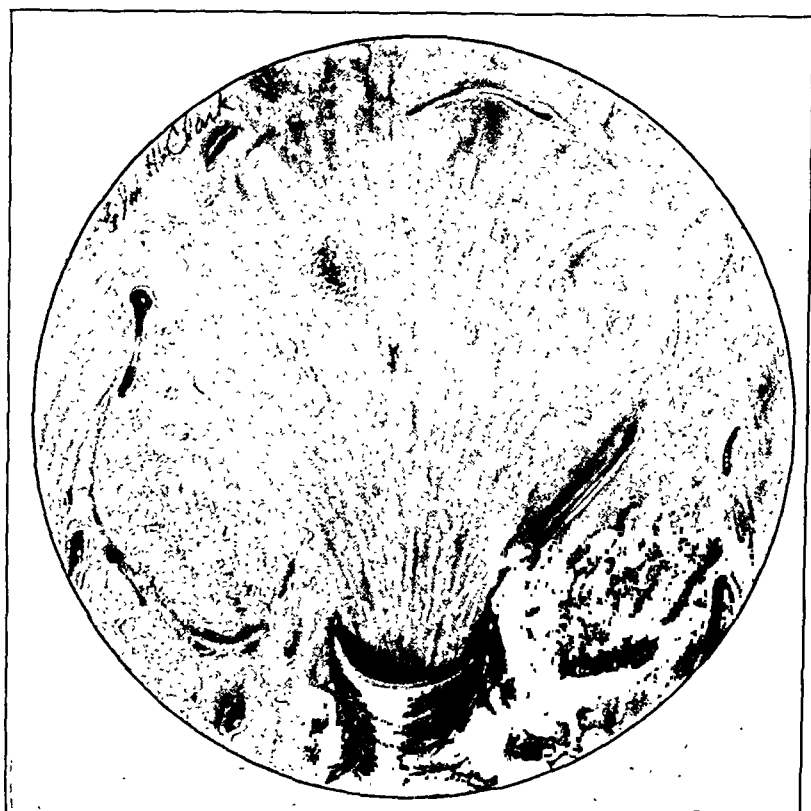


FIG. 3.—Drawing of the pyramidal portion of fresh kidney, showing extensive calcium deposits.



FIG. 4.—Roentgen ray picture of the two halves of one kidney, showing calcium deposits in parenchyma.

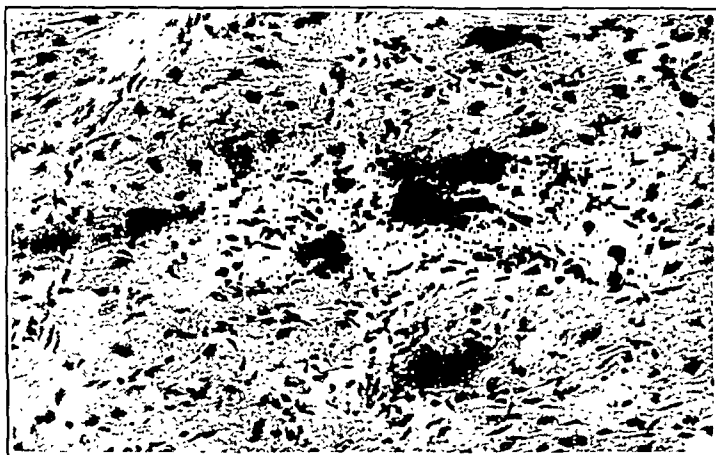


FIG. 5.—Calcification of muscle cells and arteries of the heart. The calcium is seen as fine granules and masses.



FIG. 6.—Figures 6 and 7 are from two other instance of hyperparathyroidism observed in the Duke Clinic. The delicate rosette-like mottling, due to parenchymatous calcium deposits (nephrocalcinosis) is probably pathognomonic of hyperparathyroidism.



FIG. 7.—Nephrocalcinosis.

organs and the arteries of medium and arteriolar size. Extensive myocardial injury and necrosis. Chronic tubular and glomerular nephritis with extensive medullary calcium deposits. Hepatic focal necrosis."

Calcification was present in the kidneys (Figs. 2, 3 and 4) and myocardium (Fig. 5) to a marked degree, together with widespread evidences of injury to connective tissue throughout all the organs. This was seen most conspicuously in the basement membranes of the parenchymatous organs, associated with cell necrosis and calcification. Calcium deposits were also present in the stomach and lungs to a slight degree. There was widespread calcification of the media of arterioles in the heart, kidneys and lungs.

The autopsy findings in this patient parallel very closely the pathologic changes which Cantarow, Stewart and Housel² describe in dogs poisoned with parathormone.

There is no evidence that this patient's death was due directly to the kidney injury which was present; neither the blood chemistry studies nor the symptoms which she presented indicated severe renal insufficiency. Her sudden death suggested circulatory failure; and this was the conclusion of the physician in charge. McJunkin, Tweedy and Breuhaus,¹¹ in their study of acute parathormone poisoning in rats, state: "The circulatory failure which characterizes fatal cases is secondary to the degenerative lesions in the myocardium." The myocardial lesions in the patient under discussion were shown, by postmortem studies, to be widespread and severe. However, Dr. W. D. Forbus, who studied the case very thoroughly, states in the autopsy protocol: "The injury to the heart muscle seems of itself not sufficient to have produced myocardial failure. We must fall back, therefore, upon the theory of a general, severe intoxication as an explanation of the patient's death."

Dr. Fuller Albright, in a personal communication, makes the following comment: "It is my belief that your patient died of parathyroid poisoning which is a complication of hyperparathyroidism which occurs when the blood calcium rises above a certain critical point. At this critical point the serum phosphorus, instead of being low, starts going up because phosphorus is no longer diffusible at very high levels of calcium. The thing which would have alarmed me about your case was not so much the high calcium as the absence of a low phosphorus."

The peculiar manner in which calcium is deposited in the kidney parenchyma, nephrocalcinosis, as revealed by Roentgen rays, presents a picture *which is probably pathognomonic of hyperparathyroidism*. Of 6 instances of parathyroid adenoma, which have come under our observation at Duke Hospital, 3 were initially suspected of having hyperparathyroidism from the Roentgen ray appearance of the kidneys alone (Figs. 1, 6 and 7). The calcium deposit forms delicate, rosette-like shadows which we have never seen in any other condition.^{5,6}

The only case reported in the literature that resembles the one just detailed was published in 1923 by Dawson and Struthers.⁴

The patient, a man of 49, on lifting a heavy weight, felt a sudden pain in his left upper arm, which gave way with an audible crack. Roentgen ray pictures showed a fracture. Four months later Roentgen ray pictures were made of the bones and fibrocystic disease with generalized decalcification was noted. Eight months from the time he was first seen, he was suddenly seized with a heart attack and was admitted in the evening in a state of collapse with a very rapid and feeble pulse. He was too ill to give an account of himself and died suddenly the following morning. No determination of the serum calcium and phosphorus was made.

Postmortem examination showed generalized osteitis fibrosa cystica, and at the left lower pole of the thyroid gland an ovoid tumor 1 inch in length was found. The authors were totally unable to connect the parathyroid tumor with the bone changes. Calcification was found in the form of fine granules in all the internal organs and in all the tissues of the body, especially in the elastic fibers and fine connective tissue fibrils. The pathologic findings as reported by Dawson and Struthers resemble very closely, with the exception of the fibrocystic bone changes, the findings in the case reported in this paper.

Lowenburg and Ginsburg⁹ have reported the condition produced in a boy of 5 who was given 100 units of parathyroid extract daily for 6 days by mistake, 20 units having been ordered. The child became listless, drowsy, febrile and vomited now and then. The calcium rose to 19.6 mg. %. Recovery quickly ensued, with a return of the serum calcium to normal, when the parathormone was discontinued.

One point of great interest in the report of this accidental experiment is the occurrence of a considerable degree of fever as a result of parathormone poisoning. When surgeons were called in consultation to see the patient who forms the subject of the present paper, they found the temperature elevated to 38.5° C., and advised that operation be postponed. No one who studied the patient properly evaluated the grave danger indicated by the extremely high and increasing calcium level in the blood. Two days after admission the blood calcium was found to be 20 mg. %, and 3 days later it was 22 mg. %. Between the two tests the patient was examined by several observers. It is a logical inference that the inevitable palpation of what proved to be a large parathyroid adenoma resulted in more parathormone being expressed into the blood than otherwise would have occurred, with consequent increase of the hypercalcemia and toxemia. It is well known that mild manipulation of chromaffin tumors frequently precipitates attacks of paroxysmal hypertension.⁷

The calcification associated with hyperparathyroidism has been explained as a precipitation into relatively alkaline tissues of the calcium with which the plasma is supersaturated, that is, as a true

"metastatic" calcification. It is impossible to deny that this may occur, but tissue necrosis unquestionably precedes the deposit of calcium in hyperparathyroidism. Such necrosis was obvious throughout the organs in the case here reported. McJunkin, Tweedy and Breuhaus,¹¹ working with rats, and Cantarow, Stewart and Housel,² using dogs, have clearly shown that acute parathormone poisoning causes local degenerations of tissues, which are primary, and precede calcification. In their experiments such necroses were constant and widespread in the myocardium and kidneys, the great majority of regressive lesions showing no deposition of calcium, indicating that degenerative changes preceded calcium deposition.

All writers agree that parathormone in large doses is very toxic for dogs, rapidly producing weakness, anorexia, vomiting, gastrointestinal hemorrhage, respiratory distress, evidences of general circulatory failure and acute renal failure. Such animals show a hypercalcemia, nitrogen retention, dehydration, increased coagulability of the blood, and all the evidence in the urine of acute kidney damage. These are manifestations of parathormone poisoning produced rapidly by large amounts of the hormone, and, although enlightening, yet are not strictly comparable to the chronic form of parathormone intoxication, with terminal acute poisoning, as exhibited by the case herein reported. That the body can habituate itself to large amounts of parathormone was pointed out by Collip,^{3b} and has been amply proven in the treatment of surgically produced hypoparathyroidism,¹⁰ where the hormone may lose its effectiveness after a relatively short time. There is some evidence that a sufficient supply of vitamin D prevents the development of this tolerance to parathormone.¹⁰

From the clinical standpoint it is important to realize that 20 mg. % of calcium in the blood is indicative of a very critical condition. Recovery is possible if the parathyroid tumor is removed, even where the hypercalcemia reaches 22 mg. % or slightly higher. Snapper¹³ has reported one reading of 23.6 mg. %, with eventual recovery; but it is obvious from experiments on dogs and from the case here reported, that a hypercalcemia approaching 20 mg. % is evidence of a dangerous degree of parathormone poisoning. Fuller Albright advises that patients with hyperparathyroidism be placed on a low calcium diet, especially when the phosphorus tends to be high.

Conclusions. An instance of hyperparathyroidism with fatal parathormone intoxication is reported, thus filling an existing gap in the natural history of the disease.

A characteristic type of parenchymatous renal calcification is illustrated, which is believed to be pathognomonic of hyperparathyroidism.

A blood calcium level approaching 20 mg. % is indicative of severe and dangerous parathormone intoxication.

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NOTES ON CHEMICAL STUDIES OF A GAUCHER SPLEEN.

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THE presence of cerebrosides in the spleens of patients suffering from Gaucher's disease has been demonstrated by many investigators. Although the cerebroside present is normally supposed to be kersasin, Lieb and Mladenovic⁸ were able to show the presence of a small amount of phrenosin in addition to kersasin in the spleen of a 5½-month-old child with Gaucher's disease. Capper, Epstein, and Schless² also have reported the presence of phrenosin in addition to kersasin in the spleen of a child, 6 years of age, with this disease. However, they gave no details as to the method of identification.

In 1935 Horsley, Baker and Apperly⁵ reported a case of Gaucher's disease in a man 47 years old at the time of his death. The spleen removed at autopsy weighed 5890 gm. The results of a preliminary chemical analysis of a small portion of this spleen were reported at that time; but it was felt that a further analysis of the material to prove the presence or absence of phrenosin would be justified. Accordingly, a part of the spleen which had been fixed in formaldehyde was cut into small pieces, thoroughly washed with water, ground in a meat chopper and dried. The total ether and alcohol extractives were first determined and are given in Table 1 along with results obtained by other investigators.

Procedure for Cerebroside Isolation. The finely ground and dry splenic powder was first extracted repeatedly with cold acetone and

* Presented by one of us (J. S. McC.) in partial fulfillment of the requirements for the degree of Master of Science.

then with ether. The residue, which contained the cerebroside, was extracted twice with boiling 96% alcohol and filtered hot. On cooling to room temperature a white granular substance separated out. This was filtered off and the filtrate used several times to re-extract the splenic powder. The final filtrates were concentrated to about half their original volume and cooled to 0° C. A white creamy material separated out which was filtered off and combined with the previously isolated cerebroside. Further concentration and cooling gave no additional precipitation.

TABLE 1.—ETHER AND ALCOHOL EXTRACTIVES IN GAUCHER SPLEENS.

Author.	Age of patient.	Percentage of extractives.	
		Ether soluble.	Alcohol soluble.
Epstein ⁴	35 yrs.	6.7	34.95*
McConnell, Forbes and Apperly (present authors)	47 yrs.	7.0	30.4†
Bloom and Kern ¹	7.5	22.4
Lieb ⁷	3 yrs.	6.75	11.85
Lieb and Mladenovic ⁸	3½ mos.	5.2	9.3

* Calculated on the dry weight of the extracted material.

† This is the average of a number of determinations. It is slightly higher than the results obtained on a small sample of this spleen and reported in a previous paper.⁵

In attempting to purify the crude cerebroside by recrystallization from alcohol, two fractions were obtained. One fraction precipitated readily at 37° C. while the other was soluble at this temperature but separated out when the solution was cooled to 0° C. This separation into two fractions was not dependent upon the concentration of the solution, for when the 37° C. fraction was recrystallized and the filtrate concentrated and cooled to 0° C. very little material precipitated out. Similarly when the 0° C. fraction was recrystallized no precipitate was obtained at 37° C.

The fraction separating out at 37° C. was recrystallized several times from alcohol and acetone without any apparent improvement in the appearance of the product. Consequently, Klenk's⁶ method for the purification of cerebroside was resorted to. The final product obtained was pure white and when heated showed a clearing point of 178° C. which was not changed by further recrystallization. Examination of the material with a selenite plate (gippsplate) as described by Rosenheim^{9a} showed the typical refractive picture of kersin. Another sample of the crude cerebroside was purified by Rosenheim's^{9a} method and an identical product was obtained. After acid hydrolysis, sphingosine sulphate, galactose and a fatty acid which melted at 80.4° C. were obtained. This melting point agrees with that usually given for lignoceric acid, 80 to 81° C. as opposed to 101.5 to 103° C. for cerëbronic acid. Attempts at acetylation were uniformly unsuccessful furnishing further proof of the absence of cerebroside and thus of phrenosin.

Elementary analysis of the purified cerebroside with values reported by a few other investigators for kersasin are given in Table 2.

TABLE 2.—ELEMENTARY ANALYSIS OF THE PURIFIED CEREBROSIDE.

Author.	Carbon, %.	Hydrogen, %.	Nitrogen, %.
Lieb and Mladenonic ^a	69.76	11.24	
Lieb ⁷	70.74	11.35	1.98
Rosenheim ^{9b}	68.94	11.40	1.80
McConnell, Forbes and Apperly (present authors)	70.60	11.23	1.73

The alcohol soluble material which precipitated only when the solution was cooled to 0° C. was purified by Rosenheim's^{9a} method and found by clearing point and the selenite plate test to be kersasin. We have no explanation for the difference in solubility of the two kersasin fractions. However, it might be due to differences in the fatty acid part of the molecule since Chibnall *et al.*³ have shown that lignoceric acid is not a true chemical substance but a mixture of several fatty acids.

Conclusions. The cerebroside in the spleen of a middle aged man who died from Gaucher's disease has been isolated and found to be kersasin. Phrenosin was absent.

We wish to thank Dr. Paul Kimmelstiel for his many helpful suggestions during the course of this investigation.

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A CASE OF HODGKIN'S DISEASE WITH MASSIVE COLLAPSE AND CAVITATION OF THE LUNG.

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WHEN intrathoracic Hodgkin's disease is mentioned, one usually thinks of enlarged mediastinal glands that may give rise to pressure signs like cough and venous engorgement and eventually grow out of the mediastinum into the parenchyma of one or both lungs. One does not usually think of Hodgkin's disease as being able to cause such pulmonary complications as pleurisy,¹¹ hydrothorax,¹⁵ pneumothorax,^{4,9} cavitation, bronchiectasis,¹⁴ and atelectasis. Nor does one

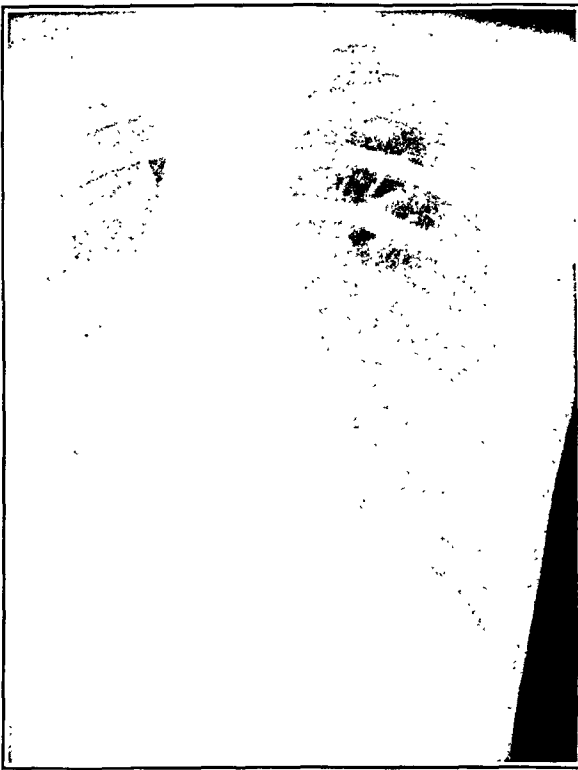


FIG. 1.—December, 1934. Partial atelectasis of right lung; small part of upper and large part of lower lobe.



FIG. 2.—May, 1935. After Roentgen-ray therapy to right chest.

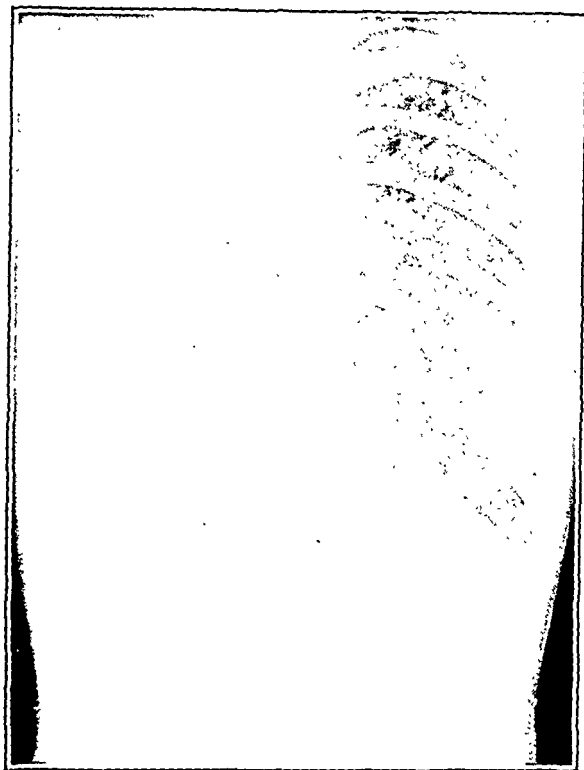


FIG. 3.—October, 1935. Massive collapse of right lung.



FIG. 4.—October, 1936. Large cavities of upper, atelectasis of lower right lung; infiltration of lower left lung.

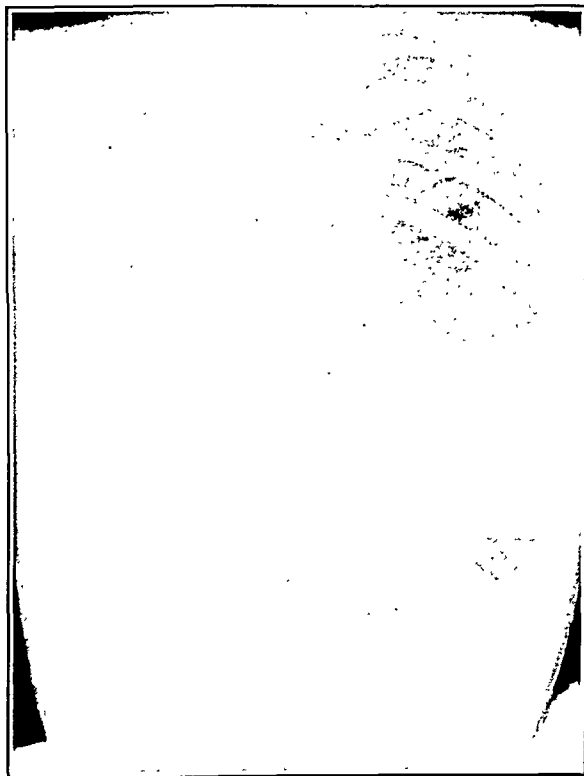


FIG. 5.—December, 1936. Massive collapse of right lung; great increase in consolidation of left lung.



FIG. 6.—April, 1937. Large cavity and atelectasis on right; infiltration and multiple cavities on left.

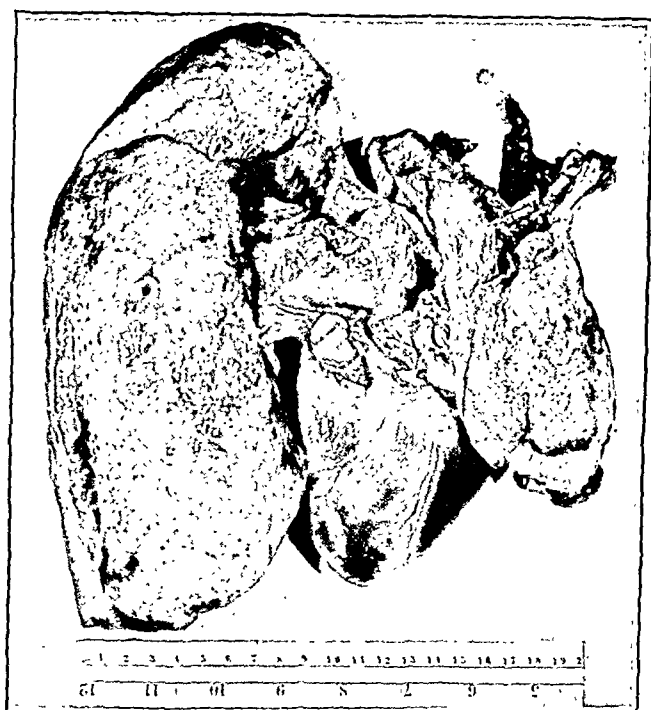


FIG. 7.—Small right lung solid with Hodgkin's granuloma except the upper portion which forms a large cavity. Infiltration of the wall and constriction of the lumen of the right main bronchus. Enlarged mediastinal glands. Dextrocardia. Large left lung studded with nodules of granuloma.

think of it as being able to produce a picture like metastatic carcinoma or miliary tuberculosis of the lung.

It would seem natural to suppose that partial or complete atelectasis due to pressure upon and occlusion of a bronchus by an enlarged mass of mediastinal or bronchial glands would be a fairly common complication of mediastinal Hodgkin's disease, especially since compression of the superior vena cava and trachea occurs so often. But this is not the case. Partial atelectasis occurs infrequently, and I can find but 2 reported cases of massive atelectasis. Both of these were complicated by pleural effusion. In every one of these cases of partial or complete atelectasis that came to autopsy the bronchial obstruction was due not to the pressure of enlarged glands upon the bronchial wall, but to the invasion of the bronchial wall by Hodgkin's tissue, granulomatous plaques being found in the bronchial submucosa and mucosa. In other words, the obstruction was inside, not outside, the bronchus.

History of Atelectasis of the Lung in Hodgkin's Disease. Although Hurd⁶ in 1922 discovered by bronchoscopy a partial constriction of the left bronchus, due apparently to the enlarged mediastinal glands of Hodgkin's disease in a woman who had cough and impaired aeration of the lung bases, real lobar atelectasis was not reported until Junghagen⁸ in 1926, Wachner¹⁷ in 1934, and Loeper and Bioy¹⁰ in 1935, each presented a case of atelectasis of the right upper lobe of the lung due to Hodgkin's disease. Atelectasis partially cleared in one and completely cleared in another following radio-therapy. Wachner's case, the only one autopsied, showed narrowing of the right upper lobe bronchus due to infiltration of its wall by Hodgkin's granuloma.

In 1932 Paviot, Levrat and Jarricot¹³ reported the first case of massive collapse of the lung due to Hodgkin's disease. It was the case of a woman of 22 with Hodgkin's disease of about 4 years' duration. She first had axillary glands; these were followed by general glandular enlargement, cough, fever, pains in chest, a right and then a left pleural effusion. There was only temporary improvement after Roentgen ray treatment over the mediastinal glands and several left thoracenteses. Just before death the dyspnea was violent, expiratory, prolonged and wheezing. At autopsy, there was found an enormous glandular mass encircling the left bronchus up to the level of tracheal bifurcation. The lining of the left bronchus was invaded and the lumen obliterated by the granuloma. The left lung was atelectatic, the atelectasis being the result both of bronchial obstruction and pleural effusion.

Moolten¹² in 1934 reported the second case of massive collapse of the lung due to Hodgkin's disease. A man of 49 had a gland in the left parotid region for 18 months, followed by fever and a cough productive of blood-streaked sputum, and rather severe dyspnea with acute attacks of wheezing. Physical examination gave signs of a massive right pleural effusion. Roentgen ray showed, in addi-

tion, a paradoxical shift of mediastinal structures towards the right. The patient being too ill for bronchoscopy, thoracotomy was done, and when the fluid was removed the lung was seen to be collapsed. An attempt to reexpand the lung by forced air pressure intra-tracheally failed. At autopsy, a polyp composed of Hodgkin's granuloma was found inside the orifice of the right main bronchus completely obstructing it. This is the first case report of massive collapse of the lung due to an endobronchial polypoid tumor composed of Hodgkin's granuloma. Moolten described another case in which partial occlusion of both main bronchi was found at autopsy. A bilateral pleural effusion probably prevented the clinical diagnosis of atelectasis. The bronchial and tracheal submucosa were infiltrated with granuloma so that the orifices of both main bronchi were narrowed and markedly obstructed.

Weber¹⁸ in 1930 and Versé¹⁶ in his monograph in 1931 discuss the pathology of bronchial occlusion and atelectasis in Hodgkin's disease of the lung. Both describe involvement of the bronchial mucous membrane with Hodgkin's granuloma.

Case Report. Miss G. H., 22-year-old unmarried Jewess, was first seen December 3, 1934, complaining of cough for 2 years. Family and past history non-contributory. Cough with production of a profuse, sometimes blood-streaked, odorless sputum began about 2 years ago; worse in early morning and late evening. Fever on and off for 2 years. Small swelling above right clavicle noted 2 months after cough began; it has increased and decreased in size but never disappeared. Profuse night sweats during last year. There was pain in right upper and lower chest with temperature 103° F. a year ago, at which time a diagnosis of pleurisy was made and a physician obtained a small amount of clear fluid from a thoracentesis. Six sputum examinations negative for tuberculosis. Roentgen ray of chest in March, 1933, showed dense shadow at right apex; October, 1933, dense shadow right base; March, 1934, dense shadow right apex. Basal metabolism in March, 1934, normal. Present weight 103, no gain and no loss. Pain in front of upper right chest for past 3 nights.

Physical Examination: T. 99.6° F.; P. 100; B.P. 117/70; Wt. 103 pounds. Well developed and nourished thin girl with a good color. Eyes, ears and nose normal. Teeth poor condition; dental caries, pyorrhea, gold crowns, bridgework. Throat negative. Tonsils removed. A node almost the size of a walnut palpable just above right clavicle and lateral to sterno-cleido-mastoid muscle; movable, not tender, not fixed to the skin. No other glands enlarged anywhere. Left lobe thyroid palpable but not enlarged. Heart: PMI felt just inside mammary line. Dullness to percussion to right of sternum in fourth and fifth interspaces extending from just medial to right midclavicular line to sternum. Heart sounds good quality, no murmurs, rhythm normal, rate rapid. Right chest: some atrophy of trapezius; motion of chest limited; tactile fremitus decreased; percussion note everywhere dull except at base where it was flat; faint breath sounds at apex, absent breath sounds elsewhere; no bronchophony or pectoriloquy. After a paroxysm of coughing bubbling and sibilant râles were heard. Left chest: hyperresonant; breath sounds normal but loud. Abdomen: negative; liver and spleen not palpable. Extremities negative. Reflexes active. A tentative diagnosis was massive collapse of the right lung. Roentgen ray of lungs* (Fig. 1) showed no active disease of left lung but an extensive

* All Roentgen ray interpretations and treatments were by Drs. A. B. Moore and E. M. McPeak, Roentgenologists at Emergency Hospital.

inflammatory process involving lower three-fourths of the right lung, multiple areas of bronchiectasis, and a central area at level of eighth rib posteriorly which appeared to be a necrosing pneumonitis, a thickened pleura in the region of the right hilus and a partial atelectasis of the right lung.

TABLE 1.—BLOOD FINDINGS.

Date.	Hgb. % (Sahli).	R.B.C. mill. per c.mm.	W.B.C. thous. per c.mm.	Differential.			
				P.	L.	M.	E.
12/ 5/34	75	3.9	11.6	56	44		
1/10/35	90	5.4	17.5	73	25	..	2
4/ 4/35	80	5.7	12.3	77	20	..	3
5/ 9/35	75	3.7	15.6	78	18	2	2
9/25/35	70	4.5	16.5				
4/13/36	70	3.8	18.3	92	8		
10/22/36	72	3.7	10.1	79	9	10	2
4/10/37	72	4.8	15.7	96	4		
4/17/37		Blood culture—72-hour cultures sterile					

December 10, 1934. In order to determine, if possible, the cause of the atelectasis, bronchoscopy was performed by Dr. D. B. Moffett. "Considerable inflammation of the right main bronchus which is increased where it divides. Thick, heavy, mucus-like pus in entire region, resembling bronchiectatic exudate, more being obtained from bronchus to lower lobe than elsewhere." Two attempts at lipiodol Roentgen films were unsuccessful because the patient coughed up all the lipiodol. However, the picture showed improved aëration of the right lung following bronchoscopy.

January to April, 1935. With the idea that we were dealing with a bronchiectatic infection or an abscess, an artificial pneumothorax in the right chest was accomplished by Dr. W. D. Tewksbury. The physical signs changed to those of a typical right-sided pneumothorax. There was some improvement in the patient's clinical condition at first but cough persisted, a chain of new glands appeared in the right neck, and there was 6 pounds loss of weight. A biopsy of a cervical gland (April 27) was reported upon as follows (Dr. J. W. Lindsay): "On section the gland is hard and gristly. The cut surface is apparently largely fibrous tissue. Microscopic section shows dense fibrosis with irregular islands of lymphoid elements. The follicular structure has been destroyed and there are great numbers of eosinophilic and single and multinucleated giant cells, the latter typical Sternberg-Reed type. Diagnosis: Hodgkin's Disease." We had not thought of Hodgkin's disease before this report.

May to September, 1935. There was an aggravation of the atelectasis after the pneumothorax air was absorbed. Following Roentgen-ray therapy to the right chest and neck there was great improvement in signs and symptoms, but Roentgen ray (Fig. 2) May 15 showed still some infiltration in middle third of right lung. There were resonance, fremitus, and bronchovesicular breathing at right upper lobe, dullness and absent breath sounds right lower chest, and disappearance of enlarged glands. In a week aëration of right upper lobe had disappeared. After further radiotherapy to right chest (June) there was an increase in density of upper right lobe with the appearance of multiple small cavities. During the summer the patient had pain in back of neck extending down to shoulders and arms, fairly constant afternoon fever, though there was one afebrile period lasting a week, cough with thick yellow profuse sputum daily with paroxysms morning and evening.

October, 1935, to May, 1936. Following another course of radiotherapy to the right chest (September and October) there was a great aggravation of symptoms. Roentgen ray (Fig. 3) October 23 showed complete atelectasis on right side with heart and mediastinum drawn completely to this

side. The patient walked into my office and showed the following signs: T. 104° F.; P. 166; R. rapid; B. P. 90/70; Wt. 90 pounds. No enlarged glands. Trachea to right. Right upper chest sunken in. PMI 4 cm. from MCL in 5th i.s. Heart racing, gallop rhythm, sounds as well heard to right as to left of sternum, no murmurs. Right lung: flat everywhere except for slight resonance over upper lobe behind and between scapula and vertebræ where breath sounds were tubular. Elsewhere breath sounds either very faint or absent. Left lung clear. Abdomen negative. She was sent home to bed immediately. (There was no further radiotherapy to the chest but several treatments to the cervical glands periodically. The glands always responded well to treatment.) She was ill at home during November and December. The cardiac p.m.i. was found in 3rd i.s. in right mammary line, there being no cardiac dullness in the left chest. Physical signs otherwise remained the same. Cough, sputum, and fever were constant.

June to December, 1936. By June 2 cavities had appeared in right apex and there was a beginning infiltration at left hilus. Roentgen ray (Fig. 4) October 9 showed some decrease in consolidation of right lung with large cavities and a more marked involvement at left base. Amphoric breathing at apex. Roentgen ray (Fig. 5) December 9 showed complete consolidation on right with a great increase in consolidation at left base. Physical signs were: cardiac p.m.i. in 2d, 3d and 4th i.s. on right side in M.C.L.; gallop rhythm. Dullness and faint amphoric breathing over right lung, an increased expiratory phase in left axilla.

January to May, 1937. Dyspneic, glands, T. 98.8° F. to 102° F.; P. around 130; R. around 30; B. P. 110/80; Wt. 87 pounds. In bed most of time. Râles at base of left lung followed later by prolonged and grating expiration, expiratory sonorous râles and dullness. The right lung was dull, with tubular breathing at apex and absent breath sounds elsewhere. Clubbing of fingers. On April 9 a severe dyspnea brought on by coughing. Respiratory wheezes very loud. Pulse 150, respiration 46. Ambulance to Emergency Hospital where she stayed until April 25. In an oxygen tent for most of hospital stay. The oxygen immediately cleared up the dyspnea. Physical signs about the same except that there was amphoric breathing over most of right lung and loud wheezing over the left. Morphine used for the first time. Afebrile for last 6 days. A portable Roentgen ray (Fig. 6) April 10 showed atelectasis on the right with practically complete destruction of lung tissue, and multiple cavities on the left with no definite consolidation noted. After her return home glucose intravenously cleared up an attack of vomiting on April 30. On May 24 there was difficult respiration and twitching of the extremities, followed by coma and an uncountable tachycardia. No response to adrenalin. The heart stopped a minute after the respiration.

Two urine examinations (December 5, 1934 and April, 12, 1937) were essentially negative. Sputum negative for acid-fast bacilli (December 16, 1936), cultures positive for non-hemolytic streptococci, *Strep. viridans* and *S. albus*. Positive for monilia albicans (January 13, 1937). (See Table 1 for blood findings.)

AUTOPSY (Dr. E. C. Rice). Body is that of an emaciated white female, apparent age 30 years, estimated weight 90 pounds. The muscular development of the right chest seems less marked than the left. A mass of enlarged lymph nodes can be palpated in the right anterior axillary line. **Thorax:** On reflecting the pectoral muscles the hyperplastic lymph nodes are found to be much enlarged and have a grayish homogeneous appearance, averaging 1.5 cm. in diameter. **Thymus:** rudimentary. **Mediastinal and Bronchial Lymph Nodes:** Are markedly enlarged, relatively firm and of a grayish-white homogeneous appearance. The mediastinal form an irregular mass measuring roughly 5 by 3 by 2 cm. The bronchials are likewise

enlarged and are intimately associated with the infiltrating new growth involving the lungs. *Pleural Cavities*: The right has been obliterated by the extensive change involving the corresponding lung. Light adhesions bind the lower lobe of the left lung to the adjacent lobe and the parietal pleura. *Lungs—right* (Fig. 7): Only a small portion of the lung remains, being densely bound to the parietal pleura and a mass of enlarged lymph nodes at the apex. A cavity filled with green pus is found involving the greater portion of the upper and middle (?) lobes, very little lung tissue remaining. The lower lobe is represented by a firm mass about the size of an adult male fist. On section, it is made up of a cartilaginous like mass of gray tissue which has infiltrated and practically destroyed this lobe. The right bronchus is narrowed 2 cm. below the bifurcation of the trachea to a diameter of 3 mm. due apparently to an infiltration of the wall at this point. The tube below contains grayish-green purulent material. The *left lung* (Fig. 7) shows compensatory hypertrophy. Its surface is a light grayish-pink. A number of firm areas can be felt throughout the upper lobe, which is air containing. The lower lobe is firm with some tissue along the lower border showing less density. On section, the upper lobe is infiltrated by a number of gray nodules, averaging 5 to 10 mm. in diameter, mostly in the lower portion. The lower lobe has a mosaic-like appearance due to massive infiltration of grayish homogeneous fairly firm masses. These vary in diameter from a few mm. to 3 cm. Very little lung tissue remains. Numerous cavities are present, filled with greenish-gray purulent material. The largest measures 4 cm. in diameter and is adjacent to the hilum. The bronchi contain thick gray muco-purulent material. *Pericardial Sac*: Drawn to the right by adhesions. The fluid is of normal amount, no cardiac adhesions being noted. *Heart*: Is of normal size, being situated largely in the right thoracic cavity. The epicardium contains a number of rather firm yellow areas along the coronary vessels and near the base of the heart. The myocardium is flabby and pale. The mitral ring is thickened. **ABDOMEN**: *Peritoneal Cavity*: No fluid or adhesions. *Liver*: moderately enlarged, fatty and passively congested. *Spleen*: moderately enlarged, fairly soft. Beneath the capsule are a number of grayish-yellow areas, approximately 5 mm. in diameter. The pulp is relatively firm and deep reddish-brown. *Adrenals*: enlarged, firm, congested medulla. *Kidneys*: normal size; left capsule strips with resistance, roughened; they section with increased resistance, the cortical and medullary portions not being well differentiated, the tissue dull reddish-brown color; there is probably some cloudy swelling and fibrosis. *Retroperitoneal lymph nodes*: a mass 3 cm. in diameter found at level of left renal vein. *Gall bladder, pancreas, g. i. tract, bladder and generative organs*: normal.

Anatomical Diagnosis: 1. Generalized lymphadenopathy with metastasis to lungs, bronchus and spleen (Hodgkin's disease). 2. Pleural adhesions, bilateral. 3. Cavitation of lung, right. 4. Hypertrophy of lung, left. 5. Chronic bronchitis. 6. Dextrocardia. 7. Subacute or chronic nephritis. 8. Malnutrition.

Microscopic (Dr. J. W. Lindsay): *Bronchus*: Marked increase in connective tissue throughout the wall. The mucosa is somewhat hyperplastic but uniform. Throughout the section and particularly in the mucosa, dense infiltration by round cells and a few neutrophils. Eosinophils are not common nor are giant cells seen. *Diagnosis*: Chronic bronchitis (Hodgkin's disease?). *Lung*: Only occasionally can an alveolar pattern be recognized, the architecture being largely replaced by dense fibrous tissue which is extensively infiltrated by round cells, a few neutrophils but many eosinophiles. Giant cells of the Reed-Sternberg type are common. A few areas of necrosis are noted. *Diagnosis*: Hodgkin's disease. *Heart*: Marked edema, sparse infiltration by round cells and considerable degeneration. *Spleen*: Diffuse and marked fibrosis with considerable loss of architecture.

Dense infiltration by leukocytes (round cells, neutrophils, eosinophiles) and scattered areas of degeneration. *Liver*: Marked fatty change and irregular round cell infiltration in the portal spaces. *Adrenal*: Parenchymatous degeneration and moderate edema. *Kidney*: Marked edema, considerable parenchymatous degeneration and sparse round cell infiltration. *Pancreas*: Marked edema. *Lymph node*: The follicular pattern is often almost completely disrupted by extensive fibrosis, round-cell and eosinophilic infiltration. Numerous Reed-Sternberg giant cells are noted, the picture being quite characteristic of Hodgkin's disease.

Discussion. There are several interesting points in this case worthy of discussion.

Diagnosis. The difficulty arose from not thinking of Hodgkin's disease as a possibility and attention being focussed on the lung to the exclusion of the supraclavicular lymph gland.

Mechanism of Atelectasis. The variability of the atelectasis was striking. Within 5 or 6 months (history) the atelectatic right upper lobe became normal and the right lower lobe became atelectatic, and *vice versa*. In other words, the mechanism that caused the obstruction was inconstant in its behavior. Following bronchoscopy, which gave no evidence of bronchial obstruction by enlarged glands, the atelectatic right lower lobe contained a small amount of air. Following a productive cough there were bubbling and sibilant râles over the collapsed lobe. In other words, when mucus was aspirated or coughed up the bronchial obstruction became incomplete. Finally there was neither Roentgen ray nor postmortem evidence of a great enlargement of mediastinal glands, the autopsy showing no bronchial obstruction from the enlarged glands that were present. It would seem, therefore, that the bronchial obstruction was not due to mediastinal glands but rather to a tenacious, mucopurulent exudate⁷ arising from the severe bronchitis secondary to direct involvement of the bronchial tube with Hodgkin's disease. Constriction of the bronchial lumen was produced by a Hodgkin's infiltration into the bronchial wall, the bronchitic exudate changing constriction to obstruction. This explanation would account for the variability of the atelectasis, the slight aëration after bronchoscopic aspiration of mucus, and the occasional presence of râles over the affected lobe during a paroxysmal cough productive of large amounts of tenacious sputum. As time went on more and more of the parenchyma undoubtedly became infiltrated so that eventually the entire lung was solid with granuloma. With all bronchi, bronchioles and alveoli obliterated by granuloma the lung would be atelectatic even if its main bronchus were not obstructed.

Moolten¹² has recently discussed the bronchitis that is so typical of Hodgkin's disease of the lung and that had previously been described by Ziegler, Versé and others. It "may appear to the pathologist as a simple chronic or acute bronchitis. . . . Frequently, however, the specific nature of the bronchitis is suggested by plaque-like opacities in various parts of the mucosa or by elevated areas or bulky nodular outgrowths which narrow the lumen considerably."

Response to Roentgen Ray Therapy. There was some clearing of the atelectasis with great clinical improvement following the first Roentgen ray treatment to the affected lung. When this was repeated 4 months later the patient became very ill with a severe reaction, characterized by vomiting, high fever, and massive collapse of the lung. The lung had become resistant to Roentgen ray therapy. Radiation of the chest was not attempted again. On the other hand, response of the neck glands to radiotherapy was always satisfactory.

Cavitation of Lungs. This has been several times reported as a complication of Hodgkin's disease of the lung parenchyma.^{1,18} Thought at first to be due to a necrosis from radiotherapy, it has since been described as occurring spontaneously.¹⁷ In the case under discussion multiple small cavities were described by the roentgenologists immediately after the first intensive radiotherapy to the right chest in May and June, 1935. Two cavities in the right apex appeared a year later (Fig. 4), 8 months after the second and last course of radiotherapy to the chest when massive collapse was first noted. No doubt necrosis existed and cavitation was potential during the period of massive collapse. From these two examples it would have appeared that cavitation was caused by radiotherapy. On the other hand, multiple cavities eventually occurred in the left lung which at no time had been exposed to radiation (Fig. 6).

Fungus Infection. The finding of monilia albicans in a culture of the sputum probably has no pathologic significance in this case. The association of moniliasis⁵ and of torulosis^{2,3} with Hodgkin's disease has been reported.

Summary. The clinical course and autopsy findings of a young woman with Hodgkin's disease complicated by atelectasis and cavitation of the lung are given in some detail. Comparable cases reported in the literature are briefly summarized, and the mechanism of atelectasis and cavitation is discussed.

The author wishes to express his appreciation of the help given him in the study of this case by those already mentioned in the text (particularly by Drs. J. W. Lindsay, E. M. McPeak, A. B. Moore and E. C. Rice); by Drs. L. Hamman, W. T. Longcope and W. G. MacCallum, of Baltimore; and by Miss Anne Hill, his secretary.

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VENOUS BLOOD PRESSURE MEASUREMENTS DURING SYNCOPE CAUSED BY A HYPERIRRITABLE CAROTID SINUS REFLEX.

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SYNCOPE caused in some individuals by the hyperactive carotid sinus reflex has been receiving deserved emphasis lately.^{1,3-5} While much information concerning this important reflex continues to accumulate, many of its aspects still intrigue investigators. This report embraces the venous blood pressure findings before, during and after the syncope induced by carotid sinus pressure.

With an abnormally sensitive carotid sinus—the bulbous dilatation at the bifurcation of the common carotid artery—an increase in intrasinus pressure often causes syncope, with or without cardiovascular changes. Weiss and his colleagues⁶ have ably classified the types of sinus response. These are: 1, the vagal type, characterized by sino-auricular or auriculo-ventricular block with its resultant asystole and syncope; 2, the depressor type characterized by marked drop in blood pressure unassociated with arrhythmia; and, 3, the cerebral type, in which syncope occurs without changes in the cardiovascular system or total blood flow through the brain.

In 8 such cases we have had the opportunity of determining the venous blood pressure during induced carotid sinus syncope.

Under basal conditions, with the normal individual in a recumbent position for at least 15 minutes, the normal venous pressure registers between 4 and 6 cm. of water, while the upper normal limit does not exceed 11 cm.²

Method. We employed the usual sterile apparatus for determining venous blood pressure, consisting of an 18-gauge needle connected by rubber tubing to the short right-angled arm of a water manometer graduated in millimeters and filled with sterile physiologic saline. Although ordinarily, when venous pressure is determined, the patient lies recumbent, with the arm on a level with the right auricle, our patients were tested while standing.

This change was necessary (except in 1 case) because the horizontal position frequently abolishes the syncope and other effects of a hyperirritable carotid sinus reflex. One of the patient's arms was held horizontally outstretched by an assistant, on as nearly a level with the right auricle as possible. The needle was inserted into the vein. The saline filled manometer was then attached. The height of the saline column, indicating the venous pressure was recorded. On the other arm a sphygmomanometer registered the arterial blood pressure. Then digital pressure was made over that portion of the carotid artery from the cricoid cartilage to the angle of the jaw. The patient was supported by a second assistant to prevent falling and displacing of the apparatus. Venous and arterial blood pressure readings were made throughout.

Our clinical material comprised 8 patients with a hyperirritable carotid sinus reflex. There were no anomalous differences in the arterial or venous blood pressures in either arm.

A brief summary of the data in each case follows:

CASE 1.—*Vagal and Depressor Sinus Response*. A. B., male, aged 24. Initial standing pulse 70, arterial blood pressure 120/80 (left arm), venous blood pressure 12 cm. water (right arm). Right carotid sinus pressure maintained for 10 seconds caused a decrease in the pulse from 70 to 22, a fall in arterial blood pressure from 120/80 to 80/60 and a generalized clonic convulsion and syncope lasting 6 seconds.

The venous blood pressure was unchanged until the convulsion when it rose from 12 cm. to 14 cm. It returned to its original level as soon as the convulsion ceased.

As in this patient carotid sinus pressure would invoke syncope even were he horizontal, the experiment was repeated in this position.

With the patient horizontal the initial pulse was 68, the arterial blood pressure 110/70, and the venous blood pressure 8 cm. water.

Right carotid sinus pressure caused a decrease in the pulse from 68 to 30, a fall in arterial blood pressure from 110/70 to 95/65 and a generalized clonic convulsion.

The venous blood pressure was unchanged until the convulsion when it rose from 8 cm. to 11 cm. It returned to its original level as soon as the convulsion ceased.

CASE 2.—*Vagal and Depressor Sinus Response*. J. C., male, aged 70. Initial standing pulse 80, arterial blood pressure 130/80, venous blood pressure 9 cm. water.

Pressure over either carotid sinus caused a decrease in the pulse from 80 to 60, a fall in arterial blood pressure from 130/80 to 80/60, and a generalized clonic convulsion and syncope.

The venous blood pressure was unchanged until the patient was actually convulsing when it rose from 9 cm. to 12 cm. It returned to its original level as soon as the convulsion ceased.

CASE 3.—*Vagal and Depressor Sinus Response*. A. Br., male, aged 57. Initial standing pulse 84, arterial blood pressure 108/80, venous blood pressure 10 cm. water.

Right carotid sinus pressure caused hyperpnea, disappearance of the pulse, a fall in arterial blood pressure from 108/80 to 60/? and a generalized convulsion and syncope.

The venous blood pressure was unchanged until the onset of hyperpnea when it rose from 10 cm. to 12 cm. and during the convulsion it rose to 13 cm. It returned to its original level as soon as the convulsion ceased.

CASE 4.—*Vagal, Depressor and Cerebral Sinus Response*. W. C., male, aged 57.

Initial standing pulse 76, arterial blood pressure 90/60, venous blood pressure 15 cm. of water.

Carotid sinus pressure caused a drop in blood pressure from 90/60 to 20/?, and a decrease of the pulse from 76 to 0, clonus of the mandibular muscles, and slumping to the floor.

The venous blood pressure was unchanged.

CASE 5.—*Vagal, Depressor and Cerebral Sinus Response*. J. Co., male, aged 14 years. Initial standing pulse 78, arterial blood pressure 108/70, venous blood pressure 12 cm. water.

Right carotid sinus pressure caused a decrease in the pulse from 78 to 65, a fall in arterial blood pressure from 108/70 to 60/40 and clonus of the contralateral limbs (left arm and leg).

The venous blood pressure was unchanged until clonus developed when it rose from 12 cm. to 13 cm. It returned to its original level as soon as the clonus ceased.

CASE 6.—*Vagal, Depressor and Cerebral Sinus Response.* W. P. G., male, aged 69. Initial standing pulse 68, arterial blood pressure 140/80 (right arm), venous blood pressure 7 cm. (left arm).

Pressure over either carotid sinus for 10 seconds caused a decrease in the pulse from 68 to 30, a fall in arterial blood pressure from 140/80 to 60/20, and clonus of the contralateral arm and syncope.

The venous blood pressure was unchanged throughout, registering at 7 cm. even during the actual clonus and syncope.

CASE 7.—*Vagal and Depressor Sinus Response.* L. S., male, aged 79. Mitral stenosis and insufficiency.

Initial standing pulse 70, arterial blood pressure 120/70, venous blood pressure 17 cm.

Pressure over either carotid sinus caused a decrease in the pulse from 70 to 40 and then disappearance of the pulse, a fall in arterial blood pressure from 120/70 to 80/60, and then to zero. Blurred vision, pallor and faintness supervened.

The venous blood pressure was unchanged until the pulse and arterial tension disappeared, when the venous pressure fell from 17 cm. to 15 cm. It returned to its original level as soon as the pulse and arterial tension returned on the release of carotid sinus pressure.

CASE 8.—*Cerebral Sinus Response.* M. S., female, aged 19 years. Initial standing pulse 84, arterial blood pressure 118/74, venous blood pressure 9 cm.

Pressure over either carotid sinus for 10 seconds caused a generalized clonic convulsion and syncope, unattended by any demonstrable change in the pulse or arterial blood pressure. The venous blood pressure was unchanged until the convulsion when it rose from 9 cm. to 11 cm. It returned to its original level as soon as the convulsion ceased.

The above results demonstrated that, prior to the convulsion, there was no significant change in venous blood pressure during the induction of carotid sinus syncope, even when the arterial blood pressure or cardiac rate fell. During the convulsion, the venous blood pressure tended to rise moderately, but promptly returned to its resting level as soon as the muscular activity ceased.

Summary. In 8 patients exhibiting a hyperactive carotid sinus reflex, measurements were made of the venous blood pressure before, during and after the induction of carotid sinus syncope.

There was no significant change in venous blood pressure, prior to the convulsion. During the convulsion the venous blood pressure tended to rise moderately, but promptly returned to its resting level as soon as the muscular activity ceased.

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PRESSOR EFFECT OF AMPHETAMINE ("BENZEDRINE") ON NORMAL, HYPOTENSIVE AND HYPERTENSIVE PATIENTS.

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ONE of the most interesting of the newer chemical compounds is amphetamine* ("Benzedrine"). Its use has been suggested in a wide range of clinical conditions.

Pharmacologic investigation has established it as a sympathomimetic amine having properties in many respects similar to those of ephedrine and epinephrine, to both of which it is closely related chemically.^{6,7,14} Since such compounds usually exhibit a definite pressor effect, this characteristic must be considered by anyone using the drug therapeutically. It seemed desirable to note the effects of small doses of volatile benzedrine base, administered as a vapor, and also the effects of larger doses of the sulphate salt, given orally.

The preliminary procedure was the same in all subjects. After a complete rest period of from 10 to 15 minutes, a control blood pressure reading was taken. All readings were taken in the usual manner, using a standard sphygmomanometer with readings taken to the nearest multiple of 5. For the sake of brevity, diastolic pressures are not included in the tables, as they showed no significant variations. The pulse and, in many instances, the respiratory rate were taken simultaneously with the blood pressure.

A. Benzedrine Inhaler. Recently it has been shown that the usual dose of benzedrine obtained by inhalation from the inhaler is never more than 1 mg. in any single hour, or 5 mg. in any one day, and generally much less than these amounts.¹⁷ Compared to the dosage necessary to obtain pressor effects by oral administration, it would seem that there should be no increase in blood pressure after its therapeutic use as an inhalant. There has been, however, an isolated case reported in which it was felt that the use of the inhaler might have caused an increase in blood pressure.¹¹

In view of these facts, it seemed desirable to have more information on the effect of moderate acute overdosage with the Benzedrine Inhaler. Tests were made on 28 subjects. All were normals or ambulatory convalescent or recovered patients.

Twenty inhalations of benzedrine vapor from the inhaler were taken by the patient as quickly as possible. Blood pressure readings were taken at intervals of 5, 10, 15, 30 and 60 minutes. In a few instances, observations were continued beyond the usual 60-minute

* I am indebted to Smith, Kline & French Laboratories, who supplied the material used in this study.

period, but no noteworthy changes from the hour readings were detected. Results are shown in Table 1.

TABLE 1.—BENZEDRINE VAPOR IN NORMALS AND HYPERTENSIVES.

Patient.	Initial systolic.	Maximum variation mm. Hg in systolic pressure.	Patient.	Initial systolic.	Maximum variation mm. Hg in systolic pressure.
1 . .	100	+10	15 . .	165	+5
2 . .	100	-10	16 . .	165	-15
3 . .	110	+5	17 . .	170	+5
4 . .	110	-5	18 . .	175	-5
5 . .	115	-5	19 . .	180	+5
6 . .	120	+5, -5	20 . .	180	+10
7 . .	125	-5	21 . .	180	-5
8 . .	130	+5, -5	22 . .	190	+10
9 . .	130	+5	23 . .	200	+5, -5
10 . .	130	-5	24 . .	200	-10
11 . .	135	-10	25 . .	210	-10
12 . .	135	-5	26 . .	220	-10
13 . .	140	-5	27 . .	240	-10
14 . .	150	+5	28 . .	250	-5

Except for an occasional complaint of local irritation from too rapidly repeated inhalations, no untoward effects were experienced by the subjects.

The greatest increase in pressure recorded was 10 mm. Hg, which was observed in 4 subjects; the greatest decrease was 15 mm., observed in 1 subject. The majority showed no change or a slight increase or decrease of 5 mm. No consistent change in pulse rate was noted nor did there appear to be any relationship of pulse rate to change in blood pressure.

Discussion. The 20 inhalations so administered should contain, according to the calculations of Simpson and Simon,¹⁷ from 0.4 to 4 mg. of volatile benzedrine base. This moderately acute overdosage was found to raise blood pressure only slightly in a few instances. It would appear that except in extreme overdosage any rise encountered in the therapeutic dose range must be in patients hypersensitive to the compound. Such individual hypersensitivity is occasionally encountered with all sympathomimetic amines.

B. Benzedrine Sulphate. Following its original therapeutic use in narcolepsy,¹⁵ the clinical application of benzedrine sulphate has been greatly extended. It has been used in a wide dose range, the average single dose being 5 to 20 mg. Many observations on the pressor effect of benzedrine sulphate have been made. Alles¹ noted a rise in systolic pressure of 40 mm. after oral administration of 50 mg. in man. The effect appeared to be more prolonged than is usual with drugs of this type.

There appears to be a great variation in pressor effect in different individuals. Myerson, Loman and Dameshek¹² found with 40 mg. taken orally that the increase varied from 8 to 64 mm. systolic; while Davidoff and Reifenstein³ found with 10 to 30 mg. dosage that systolic pressures varied from an actual decrease to an increase

of 80 mm. Anderson and Scott,² Hill⁸ and Storz and Kirk¹⁹ observed some increase with 20 mg. Storz and Kirk found no increase in any case with 10 mg., but Hill,⁸ and Gwynn and Yater⁵ observed increased pressure with this dosage. Smith and Chamberlin,¹⁸ however, state that doses of less than 30 mg. usually cause little increase in blood pressure; and many investigators have reported that there is little increase with 20 mg.^{4,16,20,21}

With oral administration the maximum blood pressure effect is usually evident in about an hour and is maintained 2 to 8 hours.

In general, it appears that the lower the initial blood pressure, the greater the percentage increase following an effective dose of benzedrine sulphate. Korns and Randall⁹ and Davis and Shumway-Davis¹³ used benzedrine sulphate in the treatment of postural hypotension.

Prolonged administration does not seem to change the resting blood pressure,^{8,20} although Donley,⁴ in treating an agitated depressive, found an increase of 40 to 50 mm. which developed after 2 weeks' therapy; and Lesses and Myerson¹⁰ in treating an obese patient found a decrease from 154 mm. systolic to 104 mm. after 25 weeks' therapy.

Because of the wide variation in blood pressure effects reported, it seemed of interest to obtain additional data on the effects of 10 to 30 mg. oral doses of benzedrine sulphate. Since some authors have felt that the drug might be contraindicated in hypertension, more hypertensive than normal subjects were included in the study.

Results of Oral Administration. Following oral ingestion of benzedrine sulphate in amounts varying from 10 to 30 mg., pressures were taken at regular intervals for a period of 1 hour, and occasionally longer (Tables 2 and 3).

TABLE 2.—BENZEDRINE SULPHATE IN HYPOTENSIVES, NORMALS AND HYPERTENSIVES.

Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.	Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.
<i>Dose, 20 mg.</i>							
1 .	90	+20	30	10 .	155	-5	15
2 .	90	+10	15	11 .	165	+5	15
3 .	95	+5	15	12 .	170	-10	15
4 .	100	-10	60	13 .	180	+20	15
5 .	110	+5	30	14 .	180	-5	15
6 .	115	+5	15	15 .	190	+10	30
7 .	120	0	..	16 .	190	0	..
8 .	120	+10	15	17 .	200	-10	30
9 .	125	-5	30	18 .	220	0	..
<i>Dose, 30 mg.</i>							
19 .	85	+35	30	9 .	125	+5	15
1 .	90	+30	30	11 .	170	+20	30
4 .	100	+15	60	20 .	170	+5	30
5 .	105	-5	15	21 .	180	+30	60
6 .	115	+10	15	17 .	195	+25	60
7 .	120	+10	30	22 .	195	0	..
8 .	120	+10	15	23 .	200	-10	15

TABLE 3.—BENZEDRINE SULPHATE IN WARD PATIENTS.

Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.	Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.
<i>Dose, 10 mg.</i>							
1 .	150	-15	45	6 .	160	+5, -5	45, 60
2 .	155	-15	45	7 .	180	+5	30
3 .	155	-10	45	8 .	200	-10	30
4 .	160	+10	30	9 .	210	+10	60
5 .	150	-10	30	10 .	210	-25	60
<i>Dose, 20 mg.</i>							
3 .	145	+10	45	7 .	170	+5	45
11 .	150	+10	45	15 .	170	-10	30
12 .	150	+30	45	16 .	170	-20	30
13 .	150	-15	45	17 .	170	-20	30
14 .	150	+10	45	18 .	180	+10	30
4 .	155	-5	30	19 .	190	+20	30
5 .	155	-25	45	8 .	200	+10, -10	45, 60
1 .	160	-10	30	9 .	200	+15	45
2 .	160	-10	30	10 .	200	+5	45
6 .	160	+10	45	20 .	200	+10	30

Benzedrine sulphate in doses of 20 and 30 mg. was administered to 23 volunteer subjects and ambulatory convalescent recovered hospital patients. Some of them received both amounts.

1. With 20 mg. administered orally, 5 of 18 subjects showed a blood pressure increase of 10 to 20 mm. Two of these were hypertensives. An increase of 20 mm. occurred in only 2 subjects. Three subjects showed a decrease of 10 mm., while the majority showed an increase or decrease of 5 mm.

2. With the 30-mg. dose, 9 of 14 subjects showed an increase of 10 to 35 mm. Three of these were in the hypertensive group. A 35-mm. increase occurred in only 1 patient who had an initial blood pressure of 85. The majority showed an increase of 10 to 25 mm., although 2 subjects showed a slight decrease. In 7 of the 9 who received both 20 and 30 mg., the blood pressure was from 5 to 35 mm. higher with 30 mg. than with 20 mg.; in Subject 8 the effect was the same, and in Subject 5 the blood pressure fell 5 mm. after 30 mg., although it had risen 5 mm. after 20 mg.

The effect of doses of 10 to 20 mg. was observed in 20 hospitalized patients suffering from a variety of diseases (diabetes mellitus, chronic nephritis, malignancy, cardiac decompensation, postoperative convalescence, and so on) who were in nearly every instance confined to bed. They were purposely selected as being in a poor state of health. All exhibited some degree of hypertension.

1. With 10 mg. a rise of pressure of 10 mm. was recorded in 2 of 10 subjects. This was the greatest increase recorded in this group. One subject showed a fall of 25 mm., while the majority showed no change or a slight rise or fall.

2. With 20 mg. there was a rise of 10 to 30 mm. in 10 of the 20 cases. In the only patient showing a 30 mm. increase, the initial pressure was 150. In 8 cases there was a fall of 10 to 25 mm. A decrease of 25 mm. was observed in 1 patient; the remainder showed an increase or decrease of 5 to 10 mm. In the group to whom both 10 and 20 mg. were given, 7 showed an increase of 5 to 20 mm. on the larger dose compared with the smaller; in 1 case the effect was the same, and in 2 cases there was a decrease of 15 mm. compared with the effect of the 10-mg. dose.

When there was a change in pulse rate it was more often an increase than a decrease. No effect on respiration was observed.

Discussion. After the ingestion of 10 mg. benzedrine sulphate by mouth, there is an occasional mild rise in blood pressure; in the present series never over 10 mm. Hg. A greater number (35%) showed an increase after 30 mg.

The data confirm the great variation in pressor response in different individuals found by previous investigators. It seems unpredictable, and does not necessarily vary with sex, age or state of well-being of the subject. Hypertensive bed patients, in a poor state of health, seem to have a greater tendency toward a fall in blood pressure after benzedrine sulphate.

There is apparently a greater tendency for the blood pressure to rise in individuals with a low resting blood pressure than in hypertensive subjects. This suggests confirmation of the rationale of its use in the treatment of hypotension.

Since 20 mg. benzedrine sulphate by mouth gave a rise in blood pressure in only 10% of the hypertensive subjects, it suggests that the clinician should carefully check the blood pressure after the initial dose and discontinue medication if it should have an appreciable hypertensive effect. In the present series, this increase has never been above 30 mm.

The incidence of blood pressure rise seems to increase with increased dosage. As a single dose of 30 mg. gives a significant rise in 35% of the cases, it is apparent that particular care should be exercised in the medication of hypertensive cases in the higher dose range.

Change in pulse rate was inconsistent and bore no apparent relation to change in blood pressure.

Summary. A. Benzedrine vapor was administered to 28 normal and hypertensive subjects by 20 rapid inhalations from the Benzedrine Inhaler, as indicated above.

1. This moderately acute overdosage had little effect on blood pressure.

2. It is concluded that therapeutic doses of the benzedrine vapor should not affect blood pressure except in cases of hypersensitivity.

B. Benzedrine sulphate was administered in doses of 20 to 30 mg. to a group of 23 hypotensives, normals and hypertensives, and in

doses of 10 to 20 mg. to a group of 20 moderately ill patients, most of whom were hypertensives.

1. The incidence of increased blood pressure after administration of 20 to 30 mg. benzedrine sulphate by mouth was, generally speaking, proportional to dosage, but varied with the individual and was apparently independent of the state of the subject's health.

2. Some subjects showed a decrease in blood pressure, in 1 case amounting to 25 mm.

3. With single doses of 10 to 20 mg., a significant rise occurred in 10% or less of the subjects. In hypertension, the drug would not necessarily seem to be contraindicated, but a careful check of blood pressure should always be made following its administration.

4. With doses of 30 mg., the incidence of significant blood pressure increase is considerably greater than with 20 mg. Great care, therefore, should be exercised in treating hypertensives with this dosage.

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BOOK REVIEWS AND NOTICES

INTERNAL MEDICINE. Its Theory and Practice in Contributions by American Authors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans, La. Pp. 1428; 35 illustrations. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

THE appearance of the third edition of this excellent work testifies to its acceptance as a standard text in its field. The subject matter has been thoroughly revised to include recent advances and developments, with new material notably on certain infections (undulant fever, tetanus, influenza, streptococcal infections, Haverhill fever, peritoneal tuberculosis, and the contagious diseases of childhood); on gastroscopy and regional enteritis; and on the rapidly expanding field of endocrinology. The volume is the work of 27 contributors (including 3 new ones who replace 2 that have died since the last edition), all of them recognized authorities in their field and, what is even more significant, all experienced as teachers in imparting their information to students. Dr. Musser is to be congratulated on the continued high merit of his text-book.

R. K.

A HISTORICAL CHRONOLOGY OF TUBERCULOSIS. By RICHARD M. BURKE, M.D., State Veterans Hospital, Sulphur, Oklahoma. Pp. 84; 1 large graph. Springfield, Ill.: Charles C Thomas, 1938. Price, \$1.50.

MORE than 500 events in the history of tuberculosis have been listed in chronological order, the subject being divided into the Ancient Period (up to 1600 A.D.), limited largely to the symptoms of phthisis; the Pre-Modern Period (up to 1800 A.D.), when physicians began examining dead body; and the Modern Period. The first part of the Modern Period (up to the discovery of the tubercle bacilli, 1882) includes the establishment of the unity of the tubercle, knowledge of its histology, and the experimental demonstration of the transmissibility of the disease. The second, and shortest part chronologically, includes the most important items of progress—knowledge of the bacteriology and chemistry of the bacillus and efficient prevention and treatment of the disease. A large folded graphic outline of the development of our knowledge of tuberculosis contains much compact information but is too unwieldy to be handled easily.

The booklet will obviously be useful to the teachers of medicine, lecturers on tuberculosis, superintendents of hospitals, secretaries of tuberculosis associations, public health officers and students of history, for whom it is intended.

E. K.

BIOCHEMISTRY FOR MEDICAL, DENTAL AND COLLEGE STUDENTS. By BENJAMIN HARROW, PH.D., Chemistry Department, City College, College of the City of New York. Pp. 383; 52 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, \$3.75.

THIS text contains a great deal of information compressed into a small number of pages. It exemplifies a recent trend in text-books of biochemistry, which is probably natural, though open to criticism—a short text,

made short not by omission but by a cramped "outline" method of presentation. The desire for brevity is apparently at odds with perhaps a stronger desire for inclusiveness. It is, of course, a natural temptation for an author to include as much recent, up-to-date information as possible.

The Reviewer believes that the present work shows good organization of material, and may prove relatively popular as a text. It will not be an "easy" text, however, due to the inclusion of certain details, typified by the following: The empirical formula of carnaubic acid; the structural formula of chaulmoogric acid; a detailed discussion of Bergmann's theory of the frequency in distribution of amino acids in a protein; presentation of equilibrium concepts in enzyme studies. Such details are, of course, of interest to the biochemist and research worker, but in a short text for the student, they lead to confusion. The Reviewer feels that judgment in omission would have improved the text greatly. There is once again a real need for a short text, furnishing essential information of physiological interest, not a compressed long text. Details might well be left to appropriate reference works, which can handle the special subjects at requisite length.

D. D.

DISEASES OF THE NOSE, THROAT AND EAR. Medical and Surgical. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., Late Professor of Otolaryngology, Rhinology and Laryngology, College of Medicine, University of Illinois, Chicago, etc., and HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Assistant Professor of Otolaryngology, Northwestern University School of Medicine, Chicago; Surgeon, Department of Otolaryngology, Evanston Hospital, Evanston, Illinois, etc. Pp. 1030; 576 illustrations and 30 plates. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$11.00.

THIS work can be recommended to student, practitioner or specialist as one of the best available works on Otolaryngology. Changes of and additions to the text of the Sixth Edition, published 8 years ago, adequately cover recent developments in the specialty.

K. H.

ESSENTIALS OF PATHOLOGY. By LAWRENCE W. SMITH, M.D., Professor of Pathology, Temple University School of Medicine; Formerly Assistant Professor of Pathology, Harvard Medical College; and, Associate Professor of Pathology, Cornell University Medical School, and EDWIN S. GAULT, M.D., Associate Professor of Pathology, Temple University School of Medicine. With a Foreword by JAMES EWING, M.D., Memorial Hospital, New York City. Pp. 886; 679 illustrations (160 plates, many in color). New York: D. Appleton-Century Company, Inc., 1938. Price, \$9.00.

THIS text-book is designed solely for the medical student and presents a rather radical departure from the standard manner of treating the subject of pathology. Emphasis is laid upon those parts of pathology which have a direct and practical clinical application. A brief discussion of the fundamental essentials of each subject is followed by the clinical history of an illustrative case, together with the gross and microscopic pathology exhibited by the organs, with illustrations. Thus, the case-history method of teaching is the basis of this book. It puts into print the more worthwhile features of an orderly series of clinico-pathological conferences.

The book abounds in colored plates and photographs and in addition to the general subject index, there is an index of the case histories and illustrations. Throughout the book are scattered blank pages for the students' personal notes. Believing that students rarely make use of an extensive

bibliography, the authors have omitted this appendage. The achievement of a close relationship between the essentials of pathology and the clinical manifestations of disease should make this an interesting book for the medical student, though it would not seem an adequate substitute for the more conventional student's text-book unless supplemented by very special methods of instruction. D. C.

KLINIK UND THERAPIE DER HERZKRANKHEITEN UND DER GEFÄSSERKRANKUNGEN. VORTRÄGE FÜR PRAKTISCHE ÄRZTE. By DR. D. SCHERF. Privatdozent in Vienna. Pp. 319; 10 illustrations. Fourth edition. Vienna: Julius Springer, 1938. Price, Paper, Rm. 7.20; Bound, Rm. 8.40.

THE author points out that he has not produced a textbook and does not cover all cardiovascular subjects, although the most important diagnostic and therapeutic problems have been stressed. The book is more representative of the best European Continental current thought and practice than any other recent publication which has come to this Reviewer's attention. It should interest the American physician who reads German easily and who wishes to supplement what our own writers of textbooks have to say by acquainting himself with the views of others. The discussion of treatment contains a number of excellent suggestions. C. W.

HUMAN PATHOLOGY. A Textbook. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland, Ohio. With an Introduction by SIMON FLEXNER, M.D. Pp. 1013; 461 illustrations (18 in color). Fifth edition, revised. Philadelphia: J. B. Lippincott Company, 1938. Price, \$10.00.

IN the 3 years that have elapsed since the appearance of the fourth edition of this well-known textbook, pathology has progressed enough to demand considerable textbook revision. "No chapter of the book has escaped alteration. The discussion of pathological pigmentations now emphasizes the significance of pulmonary silicosis. Fatty metamorphosis is presented in the light of much recent study. Amyloidosis has been reclassified and the discussion clarified. In the section on circulatory disturbances, the newer views of edema, thrombosis and pericardial adhesion have been included. There is also new material in the study of inflammation and of tumors." Other topics altered are the sections on circulatory disturbances, cardiovascular and pancreatic diseases, and those of the hematopoietic, respiratory and nervous systems. As previously, the extensive references provide easy approach for the ambitious student to a more extensive study of any subject in which he is particularly interested. This edition retains its position as unquestionably one of the leading textbooks of the subject in a language which is singularly well endowed with one-volume books in this field. E. K.

CLINICS ON SECONDARY GASTRO-INTESTINAL DISORDERS; RECIPROCAL RELATIONSHIPS. By JULIUS FRIEDENWALD, M.D., Professor Emeritus of Gastro-Enterology, THEODORE H. MORRISON, M.D., Clinical Professor of Gastro-Enterology, and SAMUEL MORRISON, M.D., Assistant Professor of Gastro-Enterology, all of the University of Maryland, School of Medicine. Pp. 251. Baltimore: William Wood & Co., 1938. Price \$3.00.

IN this volume the authors have pointed out the high incidence of secondary gastro-intestinal disorders occurring in diseases originating outside of

the digestive tract. Cardiovascular disease, pulmonary tuberculosis, focal infection, genito-urinary affections, endocrine disorders, syphilis, various deficiency states, diseases of the nervous system, skin and eyes are considered from this standpoint. The general thesis is an important one, and a compilation such as this has much virtue. The chief value of the present volume, however, is that of a catalogue. Written in the didactic manner of earlier clinical presentations, it contains many statements which will be challenged by the experimentally minded clinician. As a descriptive work, though somewhat diffuse, it contains a great deal of value; as a stimulus to clinical investigation it is scarcely provocative. K. E.

LABORATORY MANUAL OF HEMATOLOGIC TECHNIC. By REGENA COOK BECK, M.A., M.D., Formerly Instructor in Pathology and Bacteriology at George Washington University Medical School; Head of the Department of Bacteriology, William and Mary College Extension, etc. With a Foreword by FRANK W. KONZELMANN, M.D., Professor of Clinical Pathology, Temple University, Philadelphia. Pp. 389; 79 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, \$4.00.

CAREFULLY planned for the student technician, Dr. Beck's manual will also prove a valuable *vade mecum* of hematologic methods for experienced technicians, medical students practicing physicians and instructors. The selection of techniques is sound, the range is comprehensive, and the material is up to date. The style is clear and terse. Of particular value are the sections dealing with bone marrow examination, vital staining, the various erythrocyte and leukocyte indices and the hematology of exudates, transudates, and spinal fluid. The illustrations are adequate despite the absence of colored plates. Review questions and a glossary of hematologic terms are useful teaching features. A foreword by Dr. F. W. Konzelmann is justly laudatory. Your Reviewer heartily recommends this manual. T. F.-H., JR.

CAUSES OF CRIME. Biological Theories in the United States, 1800-1915. By ARTHUR E. FINK, Department of Sociology, University of Pennsylvania. Pp. 309. Philadelphia: University of Pennsylvania Press, 1938. Price, \$3.00.

AFTER commenting on the lack of appreciation here and abroad of the work done by American students on human behavior, the author proceeds to a discussion of the period from 1800 to 1915, under the following headings: Phrenology; Insanity; Moral Insanity; Alcohol and Drugs; Criminal Anthropology—I. Anatomy of the Criminal; II. Physiology of the Criminal; heredity—The Jukes; Human Sterilization; Feeble-mindedness; Conclusion.

Some mention is made of the prisoner described by Charles Dickens in *American Notes*, for whom much sympathy was created here and abroad. At times, when dealing with facts, Dickens' exuberant imagination tended toward pseudologia phantastica. In 1841, Dickens visited the Eastern State Penitentiary and later described conditions there as devastating in their effects upon the inmate mind and body. Of one prisoner with whom he talked, who was subsequently known as "Dickens' Dutchman," he wrote: "A more dejected, broken-hearted creature it would be difficult to imagine. I never saw a picture of more forlorn affliction and distress of mind. My heart bled for him . . . I never saw or heard of any kind of misery that impressed me more than the misery of this man."

The Reviewer obtained the following information from the Penitentiary. Dickens died in 1870 and the prisoner was alive 15 years later. The prison

record continues: "When the novelist saw the German thief, he was serving his second term in the Penitentiary. Since then has served 12 more, or 14 in all, in the same institution. I once saw him in Quarter Sessions after he had been sentenced to a brief imprisonment in the County Prison. With tears pouring down his cheeks he begged to be sent back to the Penitentiary even though his time had to be doubled. His request was granted." The record ends with this comment: "Solitary confinement which permits people to die of old age, cannot be such a dreadful thing."

A recent writer, an extensive employer of labor, states he will never employ an ex-convict, even though unjustly imprisoned; not because he has "done time," but because of personality change consequent upon incarceration; but, he adds, if the last year of detention were spent in a prison camp or some other extra-mural environment, his objection would be overcome. Work need not so often be denied ex-convicts: The Ford Motor Company will accept, without discrimination, all former inmates who have worked in the mechanical department of the Federal Industrial Reformatory, Chillicothe, Ohio. Careful study of crime in the light of present-day knowledge, would be instructive. Keep politics—not politicians—out of prisons. Provide more and better officers to supervise those on probation or parole. Have the last year of a long sentence spent in a prison camp. Act upon the recommendations of the recent Wickersham Committee. The writings of Sanford Bates, and many others since 1915, will be found revealing as to causes of crime and of ways to lessen some of them.

N. Y.

MATERNAL CARE COMPLICATIONS. The Principles of Management of Some Serious Complications Arising During the Antepartum, Intrapartum, and Postpartum Periods. Edited by F. L. ADAIR, M.D. Approved by The American Committee on Maternal Welfare, Inc. Prepared by R. D. MUSSEY, M.D., P. F. WILLIAMS, M.D., F. H. FALLS, M.D. Pp. 95. Chicago: University of Chicago Press, 1938. Price, \$1.00.

WITH the increasing emphasis which is being given to attempt to reduce our unnecessarily high maternal mortality, the volume by Adair and his co-workers on Maternal Care Complications ought to fulfill a very useful purpose. Only three subjects are discussed, toxemias of pregnancy (written by R. D. Mussey), obstetric hemorrhages (by P. F. Williams), and puerperal infection (by F. H. Falls).

Each subject is well covered, emphasis being evenly distributed between pathology, diagnosis and treatment. The book contains no new information, but as the editor states in the preface: "This . . . volume attempts to present the essential facts relative to the three major causes of maternal mortality."

The small size of the book, its style, and the importance of its contents ought to give it a large field of usefulness. It would be well if a copy could be placed in the hands of every medical student and interne. D. M.

HUMAN UNDERSTANDING AND ITS WORLD. A Study of Societies. By K. W. MONSARRAT, Consulting Surgeon, Northern Hospital, Liverpool; formerly Dean of the Faculty of Medicine, University of Liverpool. Pp. 480; 42 figures. London: Hodder & Stoughton, Ltd., 1937; Liverpool: The University Press, 1937. Price, 15/-.

THE author of this work—a distinguished English physician and surgeon—despite a busy life of practice and teaching has found time heretofore to publish a volume of poetry as well as a number of essays on philosophical

topics. *Human Understanding and Its World* is probably the most substantial of the author's contributions to the borderline of medical literature.

The present volume is really a remarkable work, implying, as it does, a competence in sociology, anthropology, philosophy, particularly epistemology, and the physical and biological sciences, particularly physics and psychology. The book is of professional interest to students of these disciplines.

The subject treated is the historic problem of finding a place for human understanding in a theory of nature. The author shows it to be a double problem: first, the question of the rôle of human understanding in the development of theories of nature; and second, the more fundamental question of the grounds upon which the human mind can be regarded as a phenomenon consistent with the kind of theory developed. The author's method is both historical and critical. In the first section he reviews a number of the theories of nature developed during historic times, such as those developed by the genuine primitives, Amerindians and Australians, as well as those of civilized cultures, Jews, Greeks, Romans and early Christians. While the author pretends to no original contribution in these chapters, his writing rests upon an impressive scholarship. The theory to which Monsarrat devotes the greater part of his narrative is, however, one developed by the use of the experimental method. The principal relevant features of the contributions of the physical and biological sciences are reviewed in considerable detail. There is, for example, a lengthy description of the quantum mechanics as well as a considerable discussion of the organismic hypothesis as it appears in the various biological sciences. The final sections of the book treat of the problem of showing the activity of the human understanding to be consistent with the picture of nature developed by the experimental scientist.

Monsarrat's principal conclusion from the examination of the evidence from the history of cultures is that the theories of nature obtaining among peoples who lived prior to the time of the Greeks were: "a type of human reaction which proceeds to the formulation of a picture of the world in which discrimination is minimal," and that: "the elementary apprehensions which (were) used in its construction (were) formed with a minimum of reference to any standard of classification other than that of human like and dislike" (p. 12). With the Greeks appeared the first intimation of intellectual discrimination; from that time until the present, the importance of the pure intellectual operations in the development of ideas concerning nature became transcendent.

We must not suppose, however, that the products of experiment are invariably a unique and sufficient guide to the development of the theory. A most striking example of experiment confusing the theorist is the celebrated conclusion of Heisenberg that it is impossible to determine simultaneously the velocity and position of the electron. Monsarrat believes that this experiment, and the enunciation of the principle associated with it, illustrate two kinds of improper questions addressed to nature.

"The mathematician (Heisenberg) concerned himself with the fact that when he treated the electron *ideally* as a particle in the service of classical mechanics, he could make no precise statement about its position and velocity simultaneously. The first remark we make is the impropriety of asking any question which treats the participants in events singly. This question about the behaviour of the electron followed upon another already asked and answered—namely, 'What is an electron?' Answer, 'A particle.' But nothing whatever can be said of any participant in events when it has been isolated in this manner; all that can ever be said of any factor concerns its behaviour *vis-a-vis* another, and any question which involves a preliminary 'treating as' is vitiated at its beginning. This 'treating as' may, of course,

be used hypothetically, and the question may then be asked 'Does the electron behave like this other which I have defined and named a particle?'; but when the answer is 'No' the next step is not the enunciation of a principle, but the asking of a different question" (pp. 233-234). The second kind of improper question involves a less subtle argument. This question yields no answer because of certain natural circumstances which obtain in the relations between observer and observed. In the case of the quantum mechanics: "the difficulties encountered are to be assigned to the fact that except for certain facts as to structure, the state of affairs in the atom can only be inferred from radiation behaviour, and is imperfectly told by this" (p. 239).

The first improper question discussed by Monsarrat introduces a further consideration of non-experimental factors contributing to the development of an image of nature. In the first place the author takes the position that the work of the scientist (and of course of the natural philosopher) consists in describing phenomena. Monsarrat is opposed to the notion that events can be explained. Explanation involves abstraction which in turn leads to such absurdities as the first of the improper questions listed above. In the second place the author believes that the separate sciences each do no more than contribute detail to the larger picture of what might be called the total state. In the third place the definition of the total state falls completely outside the realm of experimental science because it depends upon the acceptance of one philosophical position on the mind-body problem, and the rejection of the others. Monsarrat accepts the so-called double-aspect theory of mind and body, rejecting explicitly the theory of psychophysical parallelism and implicitly the pure idealism to which his reflections appeared at times to be leading him. The place of human understanding in the image of nature is thus guaranteed; the validity of its study is supported by a series of arguments concerning the distinctions between knowledge of our own minds and the minds of others. These arguments appear to rest upon an acceptance of the historic argument from analogy. The single concept which gives unity to the world-image is the dynamic concept of power. A final section extends the consideration to the problems of social psychology and of history.

While it is hazardous to attempt more than a tentative evaluation of this remarkable book, its obvious strength and weakness may be mentioned. Its scholarship is impressive. The recognition that experiment alone is no sufficient guide to our knowledge of nature gives evidence of a careful, penetrating reflection upon the problem of knowledge. The position occupied by Monsarrat in this respect is indeed far from that taken by many experimental scientists who are completely naive in the field of epistemology, and is one which is becoming more and more recognized by those scientists who are concerning themselves with the philosophy of science. One cannot help feeling that a wide gulf separates those who believe that Heisenberg's experiment is important because of the methodological question it raises and those who believe it to be important because, as Monsarrat writes, it seems to impute a kind of perverse untrustworthiness to the atom. His analysis of societies in respect of their images of nature is a valuable addition to the literature of the subject, and one which, it might be hoped, will lead others to amplification of the detail.

We believe the weakness of the work to be implicit in the acceptance of the theory that the manifestations of mind and of body constitute two aspects of the same thing. The argument from analogy gives only apparent support to the proposition that we may have knowledge of minds other than our own. The demonstration that the argument is fallacious unhappily leads to a solipsism, provided no new attack is made on the main problem.

There is much which may be said against the proposition that scientists

are not explainers, particularly if explanation is defined as the operation of subsuming observations under laws. While it is true that the definition of scientific law is a formidable task, we do not believe it to be insurmountable, provided recognition is made in the rôle of choice and motive in the work of the experimental scientist. We might finally point out that the concept of power formulated in the closing sections of the work is one which the experimental scientist would have great difficulty in applying to the investigation of the problems of social psychology and of history. We should pause to point out that at least one historian, Henry Adams (*The Education of Henry Adams*), has already remarked on that difficulty in the case of a similar concept.

M. P.

NEW BOOKS.

Cardiovascular Disease in General Practice. By TERENCE EAST, M.A., D.M. (OXON.), F.R.C.P. (LOND.), Physician and Physician-in-Charge of Cardiological Department, King's College Hospital; Physician, Woolwich War Memorial Hospital, etc. Pp. 206; 43 illustrations. London: H. K. Lewis & Co., Ltd., 1938. Price, 10s. 6d.

Spinal Anesthesia. By LOUIS H. MAXSON, A.B., M.D., Practicing Specialist in Anesthetics; former Chief Anesthetist, Harborview (King County) Hospital, Seattle. Foreword by W. WAYNE BABCOCK, M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. Pp. 409; 69 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, \$6.50.

Chirurgie der Lungen und des Brustfelles. (Band 26 of Medizinische Praxis, Sammlung für Ärztliche Fortbildung, Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme and Prof. Dr. K. Warnekros.) By Dr. ALFRED BRUNNER, Chirurg. Chefarzt am Kantonsspital St. Gallen; Früher Privatdozent für Chirurgie und der Universität München. Pp. 282; 112 illustrations. Dresden: Theodor Steinkopff, 1938. Price, Paper, Rm. 22.50; Bound, Rm. 24.00.

Teachable Moments. A New Approach to Health. By JAY B. NASH, Ph.D., Professor of Education, Chairman of the Department of Physical Education and Health, School of Education, New York University. Pp. 243. New York: A. S. Barnes & Co., 1938. Price: \$1.50.

Carbon Monoxide Asphyxia. By CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology and Dean, School of Public Health, Harvard University. Pp. 276; 40 illustrations, and 21 tables. New York: Oxford University Press, 1938. Price, \$4.50.

The Physiology of Anesthesia. By HENRY K. BEECHER, A.B., A.M., M.D., Instructor in Anesthesia, the Harvard Medical School; Anesthetist-in-Chief, the Massachusetts General Hospital. Pp. 388. New York: Oxford University Press, 1938. Price, \$3.75.

Marihuana. America's New Drug Problem. A Sociologic Question with Its Basic Explanation Dependent on Biologic and Medical Principles. By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. With a Foreword by E. M. K. GELLING, Professor of Pharmacology, University of Chicago, and a Chapter by FRANK R. GOMILA, Commissioner of Public Safety, New Orleans, and M. C. GOMILA LAMBOU, Assistant City Chemist. Pp. 223; 13 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, \$3.00.

Practical Birth Control Methods. By NORMAN E. HIMES, PH.D., with the medical collaboration of ABRAHAM STONE, M.D. Introduction by ROBERT L. DICKINSON, M.D., Foreword by HAVELOCK ELLIS. Illustrations by IRVING GEIS. Pp. 254; 29 illustrations. New York: Modern Age Books, Inc., 1938. Price, 95c.

The Medical Clinics of North America, Vol. 22, No. 6 (Philadelphia Number, November, 1938), Index Number. Pp. 301; 21 illustrations. Philadelphia: W. B. Saunders Company, 1938.

NEW EDITIONS.

The Surgery of Oral and Facial Diseases and Malformations. Their Diagnosis and Treatment Including Plastic Surgical Reconstruction. By GEORGE VAN INGEN BROWN, D.D.S., M.D., C.M., F.A.C.S., Emeritus Professor of Plastic Surgery, University of Wisconsin; Sometime Professor of Oral Surgery and Oral Pathology, State University of Iowa, and Special Lecturer on Oral Surgery, University of Illinois, Vanderbilt University and Atlanta-Southern Dental College, etc. Pp. 778; 589 engravings containing 1019 illustrations and 12 colored plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

Manual of Veterinary Bacteriology. By RAYMOND A. KELSER, D.V.M., A.M., PH.D., Lieut. Colonel, Veterinary Corps., United States Army; Chief, Veterinary Division, Surgeon General's Office, War Department, Washington, D. C., etc. Pp. 640; 93 illustrations and 11 tables. Third Edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1938. Price, \$6.00.

Practical Otolology. By MORRIS LEVINE, M.D., F.I.C.S., Clinical Professor of Otolaryngology, New York Post-Graduate Medical School, Columbia University; Attending Otolaryngologist, New York Post-Graduate Hospital. Pp. 416, 146 illustrations and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$5.50.

Synopsis of Clinical Laboratory Methods. By W. E. BRAY, B.A., M.D., Professor of Clinical Pathology, University of Virginia; Director of Clinical Laboratories, University of Virginia Hospital. Pp. 408; 51 illustrations and 17 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.50.

Physical Diagnosis. By RICHARD C. CABOT, M.D., Professor of Clinical Medicine Emeritus in Harvard University; formerly Chief of the West Medical Service at the Massachusetts General Hospital, and F. DENNETTE ADAMS, M.D., Instructor in Medicine in the Harvard Medical School, Courses for Graduates; Associate Physician at the Massachusetts General Hospital. Pp. 846; 391 illustrations. Twelfth Edition. Baltimore: William Wood & Co., 1938. Price, \$5.00.

Clinical Laboratory Methods and Diagnosis. A Textbook on Laboratory Procedures with Their Interpretation. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories and Gradwohl School of Laboratory Technique; formerly Director of Laboratories, St. Louis County Hospital, etc. Pp. 1607; 492 text illustrations and 44 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$12.50.

PROGRESS OF MEDICAL SCIENCE

MEDICINE.

UNDER THE CHARGE OF

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ALTERNATION OF THE HEART.

SINCE Traube³⁸ first described *pulsus alternans* in 1872, an extensive literature has developed on the subject. Interest has been more widespread upon the Continent, where it culminated, in 1930 and 1932, in the appearance of several monographs^{19b, 33a} dealing extensively with all phases of the subject. Reports since that time, still predominantly European, have added somewhat to our understanding of the fundamental causes of alternation and have clarified certain aspects of the problem. With these more recent reports the present review is chiefly concerned and older contributions will be cited only as they are necessary in the interpretation of newer data.

The term, *pulsus alternans*, indicates an alternation in the force or strength of the pulse, in the presence of a regular cardiac rhythm, arising usually in the normal pacemaker. As Mines states,²⁶ it is a condition in which cardiac muscle is acted upon by evenly spaced stimuli (either natural or artificial) and responds with alternate large and small contractions. The term implies that the cause of the irregularity rests inherently in the heart—that such extraneous influences as respiratory changes in the pulse are not primarily the cause of the disturbance. *Pulsus alternans* is, then, an index of disturbed function in the left ventricle and may be used as a sign of defective action of that heart chamber. Since clinical and animal investigations⁵ have demonstrated similar disturbances in the auricles, the right ventricle, and the hemodynamic functions dependent upon these parts, the more inclusive term, *alternation of the heart*, the *herzalternans* of the Germans, is commonly used to cover in general all the phenomena of alternation related to the heart. The auricles and ventricles may be involved singly or together, either discordantly or concordantly.^{22a}

Mechanism of Alternation. Results of experimental observations have led to many theories of alternation, but these have been reduced to two general groups, first those in which all muscle fractions contract either in different or equal degrees, but with a slower phasic entry of contractions in the smaller beats, so-called *hyposystole*; and second, those concerning the failure of certain fractions of muscle to contract on alternate beats, so-called *partial asystole*.^{43a}

Katz and Feil¹⁶ stress the factors concerned in the former group, with the alternating dynamic changes of the heart produced by constantly occurring fluctuations in the circulation. As they point out, the exact cause and effect relationship is not agreed upon by the exponents of this view,^{36,40,43b} which was first postulated by Wenckebach. If it is assumed that the first small beat puts out a reduced volume of blood, leaving an increased systolic remainder, in the next beat there is an increased initial volume and tension in the ventricle, emptying it beyond normal. The residue is then reduced and a small beat follows, the cycle continuing for a variable time. The large pulse following an extrasystole, a sudden change in rhythm, and marked variations in respiration may also initiate alteration in the initial tension and diastolic volume of the ventricles and have the same effect as the small pulse of alternation. Also since diastolic pressure (the resistance to emptying) is less in the diastole preceding the large pulse than in the one preceding the small pulse, the diastolic pressure tends to hinder the emptying of the small pulse and permits greater emptying of the large pulse. The results of Katz and Feil are in agreement with such a concept and, in general, fit with those found by other observers in experimental alternation.^{15,43b} The observations relative to such dynamic changes are interesting and important in that they were carried out, not on experimental alternation in animals but upon 5 clinical cases. All consistently showed, associated with the alternating pulse, an alternation in the intensity of the heart sounds, in the duration of the isometric and ejection phases, and in the pulse gradient. The duration of total systole and of previous diastole showed no consistent alternation, although slight changes in diastole insufficient to produce dynamic changes were noted. Measurements of the various diastolic phases were not made. In systole, isometric and ejection phases alternated discordantly with prolongation of the isometric and shortening of the ejection phase in the small beats. Thus the duration of total systole was relatively constant. The pulse gradient alternated concordantly with the size of the pulse. Such results do show that the alternation is not the result of alternation in the duration of diastole, a finding which differs from the experimental results of Wiggers,^{43b} although the importance of changes in the phases of diastole are not excluded.

These results do not exclude the possibility of the failure of certain fractions of muscle to contract to cause *pulsus alternans*. The authors make it clear that they have not proved that dynamic changes of one beat alone produce the dynamic changes in the next beat and so perpetuate the *pulsus alternans*, nor that the circulatory changes initiate *pulsus alternans* mechanically. Yet it was upon the basis of the possible effects of such hemodynamic changes on the ventricular filling and diastolic tension that Wenckebach⁴⁰ concluded that certain instances of alternation of the pulse might be due to alternate deficiencies in ventricular filling and subsequent ejection. In such instances he thought the sign might not be indicative of grave myocardial damage with a bad prognosis. Although this view is not generally held today, it is indeed true that clinical experience^{22b} has shown that such a prognostic outlook is not to be expected when alternation results presumably from fatigue phenomena dependent on extreme tachycardia. A clinical problem demonstrating the point in question, occurring at a slow heart rate,

is the case report of Nussbrecher.³⁰ In this patient, palpation of the apex or radial artery disclosed a sequence of strong beats followed by two weaker ones, the second weak beat appearing somewhat premature. The blood pressure at the three systolic levels was 210, 180 and 160 mm. of mercury, respectively, with one-third, two-thirds and all the beats coming through at the respective levels. One might offer as an explanation for these findings, as Nussbrecher suggests, that the compensatory pause following the premature contraction allowed good filling of the ventricle producing a strong beat following it. However, the next normal beat had only the normal time for ventricular filling and, compared to its predecessor, was relatively weak. Such an explanation of the mechanism of alternation in this patient is similar to those just given, and did not require, as Nussbrecher states, the assumption of partial ventricular asystole. It would, therefore, reduce the prognostic significance of the finding even though the patient had heart disease. He cites a similar case described by Gravier.⁹

The experimental observations of Wiggers^{43b} favor the same school of thought and the findings are compatible with such dynamic explanations. He noted, while working on the dynamics of ventricular extrasystoles, that the beat following a large compensatory contraction was often smaller than normal, and that frequently the next few beats showed alternation which gradually diminished and disappeared. The heart muscle was presumably normal in every respect, and the alternation was conditioned entirely by the rate, not being present in normal hearts below the rate of about 140 per minute. Like other types of alternation, the smaller beats showed a slow rise in pressure with a longer isometric and shorter ejection phase than the larger beats. At the beginning of the small beats diastolic size was less and the initial tension lower, results entirely compatible with the explanation of secondary effects of alternate ventricular filling. For details of these observations the reader is referred to the original paper.^{43b} Such temporary alternation clinically, Wiggers felt, may not be due to primary derangement of the cardiac muscle and so would not presage the development of a more permanent type.

Despite the fact that all these observations appear to be compatible with a dynamic theory of *pulsus alternans*, none proves the cause and effect relationship of the findings and none rules out the possibility of the failure of contraction of certain muscle fibers as the cause. The latter is the most favored view at present. It is favored by the experimental production of alternation of the heart, demonstrated many times, by actual injury or poisoning of the heart by various chemicals, such as aconitine,⁵ digitalis,²⁹ glyoxalic acid,¹⁵ and other chemicals,²⁵ as well as following exposure and manipulation of the heart,⁵ impairment of blood supply, as in interference with coronary circulation, nervous influences,^{25,29} and production of tachycardias. Actual cardiac damage or factors predisposing to cardiac fatigue appear at work in all these procedures. Such observations raise the question whether *pulsus alternans* as seen in the clinic is always analogous to the experimental type and whether it also must always rest upon serious impairment of myocardial function.

In 1882, Gaskell,⁸ working on the cold blooded heart, concluded that when the ventricle alternates a partial asystole occurred with the

smaller contraction dependent upon a lowered excitability of certain fibers which respond not to every beat but to every other beat. There is, then, in this view no failure to conform to the all or none law, for certain fibers did not respond at all. Hering¹³ carried out his observations on the mammalian heart and reached similar conclusions. He felt that groups of fibers remained in a prolonged refractory period, permitting response only to every other cardiac cycle and resulting in partial asystole at the time of the smaller contraction. Whether this failure to contract may be confined to the time of the smaller contractions or occurs in both contractions but to a greater extent in the smaller beats is a matter of controversy. Mines²⁶ favors the latter view and sees no reason to expect that the portions of the muscle exhibiting asystole should form circumscribed masses. Such fibers may be distributed throughout the myocardium as well as occurring in circumscribed areas. Other theories besides the prolongation of the refractory phase have been proposed as possible causes of failure of fractions of the myocardium to contract. These include a reduction in irritability of these fibers to a level where the natural stimulus becomes subminimal and the incidence of local blocks which prevent the impulse from reaching these fractions.^{43a} Many of these controversial topics have been treated by Lewis.^{22c}

The observations of Green¹⁰ from Wiggers' laboratory are pertinent to the view of asystole. In dogs, he reduced the blood supply to a portion of the myocardium by intermittent clamping for short intervals of a main coronary artery. The vessel was occluded with an electromagnetic clamp for one-half to two-thirds of each heart cycle and occasionally for 2 or 3 cycles out of every 5 or 6, impairing the blood supply but not completely suppressing it. Alternation appeared in a fair number of hearts. Optically recorded myocardiograms from the affected areas showed that these portions of the myocardium did not contribute to ejection in the smaller beats and either contracted inadequately or only sufficiently to prevent stretching of the area by the increased intravascular tension. Since it seems reasonable to assume that the portion of the myocardium having an unimpaired blood supply should contract normally, Green feels that the alternate missing of contractions in the ischemic area is undoubtedly responsible for the alternating pulse shown in the aortic pressure curves. Demonstration was made in 2 curves also that contractions not only failed in the ischemic area in the smaller beats, but those that occurred in the larger beats were less vigorous. Thus it has been shown in the mammalian heart that impaired circulation may institute the occurrence of alternation and that when the failure of contraction is limited to one portion of the heart the alternation produced in the pulse cannot be distinguished from alternation involving the entire myocardium of the left ventricle. In applying these results to the theories of alternation, one can see that alternate contraction and failure to contract of segments of the myocardium, either large, or multiple and small, must be considered as a possible cause of clinical alternation either of the left ventricle or the whole heart. Since *pulsus alternans* is seen frequently at normal heart rates in patients with coronary changes, this mechanism is a most likely one, possibly involving multiple small areas in diffuse sclerosis and a large segment or segments in acute infarction. Yet the demonstration

of alternation following clinical acute myocardial infarction^{22a,37} is not *a priori* evidence that the segment of myocardium involved is alone responsible for the alternation, for, unlike in experimental animals, the coronary arteries of clinical cases with infarction may be inadequate in other portions of the heart, particularly in the stage of shock, and these portions of the heart may also contribute to the alternation detected in the pulse.

Certain of Green's observations are also important in evaluating the hemodynamic changes already given above. Myocardiographic records in dogs with both extrasystoles and impaired coronary flow showed that in the alternation following extrasystoles inherent changes in the muscle are probably important, for contraction changes occurred in alternate beats. He suggests that the relationship to changes in initial tension and length found by Wiggers are probably fortuitous and not to be regarded as fundamental determinants of alternation. The time required for recuperation rather than the dynamic changes is the factor probably dominantly concerned in producing this temporary type of alternation. Wiggers was careful to state that such dynamic factors cannot be held accountable for permanent alternation seen clinically. With the additional information added by his observations, Green questions whether any form of alternation can occur without periodic diminution or absence of contraction in some fractions of the ventricular muscle.

Clinical Aspects. The clinical aspects of pulsus alternans are concerned most importantly with its recognition and differential diagnosis, as well as its clinical significance in diagnosis and prognosis.

Recognition. There are no subjective symptoms referable to pulsus alternans *per se*. Since it is a manifestation of left ventricular damage, it will be found in those individuals displaying symptoms of disease affecting that chamber of the heart, especially angina pectoris, coronary thrombosis, aortic regurgitation, and congestive heart failure from other causes.

The methods of eliciting pulsus alternans are too well known to deserve comment. Most commonly used is that employing the blood pressure cuff. Since the systolic pressure is higher in every other beat, as the cuff pressure, previously raised above the systolic level, is lowered, at one level every other beat comes through, and as the pressure is further lowered until the second systolic level is reached, all beats come through; that is, the number of beats coming through is suddenly doubled. The degree of alternation can be expressed in millimeters of mercury difference in the two systolic levels. This may vary from about 2 mm. of mercury to the pulse pressure of the beats with the higher systolic level in most extreme grades. In the latter instance no, or little, blood is put out and consequently no, or only a slight, pulsation is produced by the weak contraction. The pulse is then slow and at half the cardiac rate. The more extreme grades of pulsus alternans are recognized by palpation alone, but this method of examination becomes useless in the minor grades.

There is one other method of recognition of pulsus alternans in common use. That is the arteriogram, or pressure pulse tracing of the radial or any other artery. This latter method requires the use of a piece of apparatus not possessed by most physicians; and, according to

White and Lunt,⁴² the alternation usually must be in the neighborhood of 6 mm. of mercury before it is discernible in the ordinary radial tracing, whereas an alternation of 2 mm. of mercury may be found by use of the sphygmomanometer.

The frequency of pulsus alternans, particularly the transient variety, is difficult to estimate. White^{41a} found it as frequently as auricular fibrillation. In an 8 months' study at the Massachusetts General Hospital, he found alternation of the pulse in 33% of all patients showing any degree of cardiac decompensation from whom a radial pulse tracing was obtained. Such tracings showed alternation in 71 of 300 patients with cardiac or cardiorenal disease. Yet reports stress its rarity, indicating that the frequency with which it is sought when blood pressure determinations are made is very low.

A sign as important both diagnostically and prognostically as alternation of the pulse should be sought for in all patients suspected of heart disease. Because practically every physician carries routinely to the bedside all the equipment necessary to make this test and because the procedure for establishing the presence or absence of pulsus alternans is carried out on these patients anyway when the blood pressure is taken, the lack of recognition of this sign lies either in ignorance or in negligence. It should be sought for deliberately in all patients suspected of heart disease when the blood pressure is taken. This is particularly true in the middle aged and elderly patient, for it is most frequent in those with hypertension, coronary sclerosis with and without angina pectoris or coronary thrombosis, as well as in other types of heart disease. For example, in one series,³⁷ 71 patients with pulsus alternans died of cardiovascular disease. With the exception of 6 patients with rheumatic heart disease and 2 with heart disease of unknown etiology, all had either hypertensive cardiovascular, or coronary artery disease. Hypertension was present in 81% of these patients and in 2 with rheumatic heart disease, making a total of 83% with hypertension. In this class of patient particular care should be taken to search for alternation following isolated premature beats, for it may present itself only at that time. Repeated search in subsequent visits should be made. It should also be remembered that alternation may occur at the systolic level and the diastolic level either singly or at the same time.

It is generally stated that the detection of alternation in the heart sounds by auscultation over the precordium is rare. White^{41a} found no significant changes in heart sounds and others have reported similar findings. Such statements have not gone unchallenged. As early as 1905 Volhard³⁹ reported recognition of alternation of the heart tones with accentuation of these changes following premature beats. With the large pulse beats the intensity of the sound was increased and the pitch became higher. Katz and Feil¹⁶ found a concordant alternation of heart sounds in their patients. The second sound was less intense in all subjects and shorter in duration in one in the smaller beats. In 2 cases a third heart sound showed alternation, more intense in the diastole preceding the small beat. Morris^{28a,b} found, in 38 patients with permanent alternation, that one-half the patients displayed an alternation in intensity and pitch of heart sounds or murmurs or both. He found these changes sometimes in the first or second sound at the apex

and at times in other valvular areas. Rarely both (first and second sounds) alternated together. More recently Cossio, Lascalea and Fong⁴ have confirmed the findings of Morris by use of phonocardiographic records. In 7 patients with pulsus alternans they found alternation of the heart sounds—in 4 the first sound and in 3 both sounds. They found, however, and this may be partially responsible for the lack of recognition of auscultatory changes, that the alternation was not constant. It occurred only at certain moments and seemed to disappear at other times. They noted further that single premature beats were followed by conspicuous alternation of the sounds as a rule.

The known abruptness of the elevation in intravascular pressure in the beginning of systole of a large beat would be expected to increase the intensity of the first sound in this beat as compared to the intensity of the same sound in a small contraction, when the rise of intravascular pressure is gradual. The same relationships in the fall of pressure at the end of systole would be expected to produce the same relative changes in the second sound of each beat. However, these observers found the reverse relationship in regard to the second sound and cite a similar case in the literature. The discordant character of the second sound they ascribe to a greater impairment of conduction of the sound to the chest wall at the end of the strong beat when the heart is actually smaller (more contracted).

Both of these groups of investigators stress the fact that alternation of the sounds must be carefully listened for or it will be missed. "The acoustic phenomenon which expresses the alternation of the sounds is in no case so conspicuous as to become evident on auscultation. Generally it is within the limits of perceptibility and if it is not deliberately sought it will be overlooked."⁴ Six of these 7 cases were detected by auscultation before any graphic record was obtained. It appears that failure to recognize alternation by auscultation over the precordium when it can be detected lies in a large part in the same reasons for its lack of recognition by use of the blood pressure cuff: it is not deliberately sought. Objective records of heart sounds showing the frequency of sound alternation must modify the view that such changes are exceptional. It is a frequent occurrence often occurring only to a mild degree easily overlooked by auscultation.

The differences to be noted when searching for alternation are in intensity and pitch. The one sound is more intense, higher in pitch, and "drier" than the same sound in the following cycle.⁴ These same authors state that a slight irregularity independent of the regular cardiac rhythm, is perceived by the ear. It is supposedly due to a real anticipation of the second sound in the cardiac cycle in which a weak first sound is produced by the shorter duration of the systole of this beat.

Differential Diagnosis. Little need be said here concerning differential diagnosis. The differentiation of pulsus bigeminus due to regularly recurring premature beats with resultant changes in the blood pressure are well known and easily ruled out by precordial auscultation for signs of premature beats and by electrocardiography. While the distance between the large and small beats is less than the distance between the small and large ones in pulsus bigeminus due to premature beats (the small ectopic beat is premature and closer to the preceding normal or large beat), any change which may be present in pulsus alternans is

the reverse due to the delayed opening of the semilunar valves and the slower pulse wave velocity of the small beat. This was first noted by Traube and, as Lewis^{22c} states, it may be conspicuous, slight or absent. The misdiagnosis of pulsus alternans for premature beats and its occurrence in several beats following a premature beat should not be confused.

Other confusing factors are uncommon. The changes produced in systolic blood pressure levels by respiration, particularly when the respiratory rate is about one-half the heart rate, are easily recognized and ruled out by controlling respiration. Possible confusion with a dicrotic pulse is easily differentiated in that the pulse would be timed at twice the cardiac rate as determined at the heart. Again, when the alternation is so severe that no ejection from the left ventricle occurs with the weak contraction, alternation will not be recognized in the pulse, but a rate exactly one-half of the heart rate will be found. This latter condition must be very rare. Excellent examples may be found in the experimental curves of Lewis.^{22c}

Alternation of the auricle has been described and recognized by alternate changes in the *a* wave of the jugular pulse. While such changes in the *a* wave may be indicative of auricular alternation, either concordantly or discordantly with the pulse, it may be due to the auricular and ventricular systoles coinciding, alternate auricular beats falling with the stronger or weaker beats of the ventricle. Under these circumstances, it cannot be taken as a measure of the force of the auricular contraction.^{22c}

Clinical Significance. Pulsus alternans is of great clinical importance diagnostically and prognostically. White^{41b} describes it as practically the only pathognomonic sign known of weakness or failure of the left ventricle. With the now recognized necessity of detecting left sided heart failure before peripheral edema and the other signs of right sided heart failure make their appearance, the increasing importance of pulsus alternans as a diagnostic aid will be appreciated. Its presence would be helpful in differentiating from left ventricular disease disorders of the lungs which produce dyspnea, as well as in following the course of such conditions as hypertension, which are known to put a strain upon the left ventricle.

From the prognostic viewpoint, patients with pulsus alternans should be divided into two groups. The first group includes those patients with alternating pulse and extremely rapid hearts, particularly paroxysmal tachycardia. Little is known of the mechanisms and associations of alternation in such instances and its prognostic value in such patients is not definitely known. When the tachycardia stops, the alternation disappears and the patient's outcome is apparently conditioned by factors other than the pulsus alternans. Whatever its significance in such patients it is not a grave prognostic sign and probably indicates an extreme burden even upon a normal heart.^{22b}

The second group consists of those patients in whom pulsus alternans accompanies a slow heart rate. In these patients the alternation generally occurs when the rate is over 90 per minute and may disappear as the rate falls to approximately 70 per minute.²¹ Here the prognosis for life is about 1 to 2 years, but exceptional instances of 5 or more years are recorded.^{21,37,44} The report of Thompson and Levine³⁷ typifies

the consensus in the literature. In 117 patients with the constant variety seen over a 12-year period, there were 71 with known dates of death. Of the 71 patients only 5 were under 40 years, and in them the average duration of life after detection of alternation was only 6 months. Those of 70 years or older lived on an average of 19 months, and further analysis disclosed that the older the patient was at the time of detection of the alternation the longer the life after detection. Analysis according to sex showed that 50 males averaged 17 months after detection; 21 females only $8\frac{1}{2}$ months.

Other interesting findings occurred in this same series. The average length of life after detection in patients with hypertension was $15\frac{1}{2}$ months, in patients without hypertension, 9 months. This conforms with Hewlett's experience.¹⁴ However, at very high pressures, this relationship did not hold. In general, then, in this group prognosis was better with hypertension, either systolic or diastolic, until very high pressures were reached. Prognosis was also more serious with frank signs of congestive heart failure, but this state in itself adds much weight to the prognosis. Likewise those with coronary occlusion averaged only $5\frac{1}{2}$ months, those with coronary artery disease and no occlusion $17\frac{1}{2}$ months. The presence of intraventricular block in the electrocardiogram did not seem to increase the gravity of the picture.

Electrical Alternans. The term, *electrical alternation*, has come to mean⁶ a regular alternation at equal intervals in amplitude or contour, or both, of the varying phases in the electrocardiogram. It can be seen that such an inclusive statement brings under the term, *electrical alternans*, a great number of electrocardiographic changes, including alternation of the *P* waves alone, which is rare, of *A-V* (*PR*) and intraventricular conduction^{2,11,27} of *R*, *S*, and *T* wave amplitude. *T* wave alternation, alone or with similar changes in the *QRS* group (particularly *R* amplitude), appears to be most frequent. *S* wave alternation is more rare.²⁴ Like the mechanical variety, it is usually transient and varies in degree and constancy, but it is less frequent. At the University of Illinois cardiac clinic⁶ the condition did not occur once in 6000 records. Another group¹¹ found it only once in 10,000 tracings. Likewise, the paucity of reports in the American literature tends to confirm the rarity of its occurrence, although the number of cases in the Continental literature^{3a,40} indicates that it is probably more frequent than American observers suspect.

In electrical alternation, problems in differential diagnosis similar to those in mechanical alternation must be considered. For example, bigeminy of ectopic beats and the effects of respiration may produce voltage alternations but these are easily differentiated by those familiar with the electrocardiogram. Such conditions as bidirectional complexes^{23,32,35} and alternating bundle branch block^{18,20} are not generally considered in the term, *electrical alternans*, although their inclusion in each case would be merely a matter of definition, and pulsus alternans has been described in alternating bundle branch block.⁷ In both, and especially the former, the prognosis has been very grave.

Although mechanical alternation is seldom accompanied by electrical alternation, the electrical variety is seldom unaccompanied by the mechanical. The pulse may alternate discordantly or concordantly with the electrocardiogram. Isolated electrical alternation, that is electrical

without accompanying mechanical alternation, has been known for years. Mines²⁶ first described it in the frog in 1913, and subsequent clinical reports had all been European until 1936 when the first American report¹¹ appeared. Since that time several additional American reports^{1,6,27} have been made. In one case¹¹ there was no alternation detected in the pulse, apex beat, or heart sounds, and the alternation was precipitated by changes in respiration. In this patient, *QRS* and *T* alternated discordantly. Autopsy showed multiple microscopic myocardial infarcts. In another, in whom *QRS* changes only were noted, small carcinomatous metastases were found in the heart. The authors concluded that malnutrition of the myocardium was responsible for the electrical disturbance and that these changes had the same significance as mechanical alternation. Alternating foci of impulse initiation and alternating paths of conduction of impulses from one focus can account for alternation in the form and height of complexes in the electrocardiogram, as Brody and Rossman¹ point out. In the past, electrical alternation like the mechanical variety has been described in experimental and clinical coronary disturbances and there has been adequate confirmation of these points by European workers. The close association of the etiologic factors causing both types of alternation, as well as the frequency of their occurrence together, indicate that they are many times probably of the same significance. Still their appearance independently from each other leaves the possibility of their having different clinical significance, particularly in forms other than those involving the amplitude of *R* and *T* waves. As yet there are not sufficient data for the adequate handling of these problems statistically. Poumailloux^{33b} feels that there are two forms of electrical alternation having different significance. Alternation of the *T* waves, with which *QRS* alternation may be associated, has the same significance as mechanical alternation, and alternation of the *QRS* complex or any of its components, which is transient, is totally unrelated to mechanical alternation. There is considerable controversy on these points.^{3b,19a}

Should electrical and mechanical alternation be expressions of the same physiologic disturbance, may we account for the occurrence of one in the absence of the other? May the same phenomenon in various instances be demonstrated best by electrocardiography and in others by mechanical means? Mines²⁶ has offered an explanation. He calls the whole musculature under consideration *V* and the muscle whose excitability is lower than the rest *v*. The latter portion must be subdivided accordingly as it chances to respond to the odd or even series of excitations. The alternating series will usually run $V-r_1$, $V-r_2$, $V-r_1$, $V-r_2$, etc., and not simply V , $V-r$, V , $V-r$. If $r_1 = r_2$ so that mechanical effects are alike, yet owing to their different positions in relationship to the electrodes, their effects on the electrocardiograms may be dissimilar. Similarly, the mechanical events may be favorable for alternation when the electrical derivations fail to show changes. Likewise, one may see that the disappearance of electrical or mechanical alternation would not necessarily be a sign of improvement, for those segments of muscle failing to respond at every other beat may so increase, rearrange, or become progressively impaired that equal effects result in each beat. Alternation would then disappear even in the face of a progressively downward course.

Feldman⁶ has added another consideration to the problem of electrical alternation. He reported electrical alternation involving the *QRS* complex and at times the *PR* interval in a patient with pericardial effusion due to carcinomatous metastases. Mechanical alternation was not detected in blood pressure determinations. Autopsy revealed no coronary disease, no extensive myocardial fibrosis and no metastases to the heart, leaving the effusion as the probable cause of the alternation.

That pericardial effusion may lower the voltage of the electrocardiogram is well known, both in experimental¹⁷ and clinical^{12,31} cases. If the hydrostatic pressure is elevated adequately in the pericardium, and this appears to occur clinically, it may lead, as shown experimentally, to interference with coronary circulation (cardiac tamponade) in the face of normal coronary arteries.^{17,34} The hydrostatic pressure developed varies widely and depends upon such factors as rapidity of filling, actual amount of fluid, and distensibility of the sac. Hence, as Feldman states, it is easily conceivable that the anoxemia thus produced may, under certain circumstances, interfere with the intrinsic circulation of certain regions of the heart muscle and thus lead to alternation. If this is true, it may be that under such conditions the alternation would have the same prognosis as the pericardial effusion, whatever its cause and extent.

One must speak with caution concerning the prognostic importance of the various types of electrical alternation. Those occurring in paroxysmal tachycardia, as in the mechanical type in this condition, have apparently a like prognosis. With slower heart rates, however, one must, in the face of its known association with serious myocardial disease, view it as an ill omen.

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PEDIATRICS

UNDER THE CHARGE OF
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PNEUMONIA IN CHILDHOOD.

PNEUMONIA in children is generally regarded as a less serious condition than pneumonia in adults. This viewpoint may be only relatively accurate. Very virulent strains of infection may occur in children and the threat against life may be equally as grave as a similar infection in adults. However, for the most part the heart, the kidneys and other organs of children are better able to withstand the toxic effects of the disease because they have not been subjected to the stresses and strains of repeated infections, overwork, overworry or dissipation that constitute the life of an adult.

In children, certain conditions may predispose to a high mortality rate. Gruninger and Droste¹⁰ point out that the death rate from pneumonia is comparatively high in children during the first year of life. In their clinic, a noticeable decrease in the mortality rate had been observed during recent years. In order to determine what factors were responsible for this decrease, they analyzed the cases of pneumonia that were cared for during the years of 1924, 1926, 1928, 1930, 1936 and during the first half of 1937. The cases totaled 1645. The mortality varied with the various types of pneumonia. In lobar pneumonia, they found that the uncomplicated involvement of one lobe healed with or without treatment. Such a type of pneumonia is not suitable for the evaluation of a therapeutic procedure. Excluding lobar pneumonias and abscess-forming pneumonias, they found that in all other types the infants with rickets had a higher death rate. They observed that the fresh air treatment produced a noticeable decrease in the mortality of different types of pneumonia. In the whooping-cough pneumonias and in the complicated bronchopneumonias the favorable

effects of the fresh air treatment could be increased by the viosterol treatment of the children having rickets. The successful viosterol treatment of pneumonia in rachitic children was further corroborated by their favorable experiences with the massive dose of vitamin D₂ in rachitic children with pneumonia.

During a 5½ year period 459 cases of pneumonia were studied by Ellenberg and Martin.⁷ Of these cases 89 were 1 year or under, and 48 between 1 and 2 years of age. Further statistical study showed that 40% were under 3 years of age, while 50% were under 4 years. The smallest number of cases were recorded in the ninth, tenth, eleventh and twelfth years of life, while the peak was reached in the first year. Lobar pneumonia was more prevalent among the male children as shown by 260 males being affected as compared with 199 females. While the comparative figures in the literature are scarce they conform to this ratio. As regards seasonal incidence, the greatest number of cases were recorded during the late winter months and the greatest morbidity for the entire period of study was found to be in March with April coming a close second, while the smallest number of cases occurred in July. During the 5½ years covered by this study the peak of morbidity occurred each year in a different month. In this series of 459 cases of lobar pneumonia 40 died, a mortality rate of 8.6%. Of these, 18 died during the first 48 hours after admission and were regarded as non-institutional deaths and this brought the mortality rate down to 4.7%. They found that the mortality rate was higher in children under 2 years. These gave a death rate of 24% as compared with 21.1% in the children over 2 years.

Nedzel¹⁴ claimed that the presence of pneumococci in the upper respiratory tract is not a sufficient cause for the development of lobar pneumonia, but that a dysfunction of the upper respiratory tract must precede the development of the pneumonia and this disturbance must be of such extent or type as to involve the whole respiratory tract and lead to the lowered resistance of certain tissues. This occurs when normal circulation of the blood is impaired. The vascular contraction of mucous membranes of the respiratory tract, which accompanies that of the skin during exposure, causes a delay in the mobilization of the defensive forces, and as a result of this disturbance in the irrigation of the tissues they become impaired and the bacteria present find a favorable field for their development. The exposure of the body to cold is a powerful factor that not only causes the contraction of blood vessels of the skin, but also, on account of the existing splanchno-peripheral balance, involves the blood vessels of the mucous membranes of the whole tract and causes stasis and edema in the lungs. Such a condition favors the multiplication of pneumococci.

Pelfort¹⁷ in discussing the frequency and localization of pneumonia in the infants under 1 year, maintained that lobar or croupous pneumonia is of frequent occurrence in the first year of life. He observed 64 cases from 1923 to 1935 among 300 children under 3 years of age with pneumonia. In this period, he followed practically every case with Roentgen studies. In this way he found 38 different localizations of the lobar distribution in 30 cases. The upper lobe of the right lung was the most frequent site of involvement. The lower and upper

lobes of the left lung came next in frequency and finally the middle and lower lobes of the right lung.

Joppich^{12a} showed in his study the variability of pneumococcic manifestations in infancy. Many times the Roentgen rays did not give an accurate picture of what was occurring. He tried to show why some types of pneumonia are lobular and some globular. Some think that the difference is due to different types of pneumococci while others think that it depends on the reaction of the human organism. Among the autopsy material several instances were encountered in which both types of pneumonia were present. This led him to believe that the question could not be answered.

According to Robertson¹⁸ very little is known concerning the optimum conditions for the inception of lobar pneumonia in the human being. That some disturbance in pulmonary function precedes the onset of this disease in the majority of cases seems probable in view of the frequency of antecedent acute infection of the upper respiratory tract, but the manner in which such infection lowers the resistance of the lung to invasion by pneumococci can only be conjectured. Directly opposed to any influence of previous infection is the fact that in a considerable number of cases lobar pneumonia develops during a period of apparent good health. He was able to produce in dogs a lobar pneumonia closely resembling that which occurs in humans. This was done by implanting pneumococci suspended in a starch-broth paste into the terminal air sacs of the animals. The pneumococci were dispersed from the site of implantation principally by the edema fluid of the early lesions which spread peripherally through the contiguous air passages and the pores of Cohn. The experimental lesions developed in practically the same manner as the disease develops in the human. He observed a striking histologic change both in man and in the dog at the time of recovery. This consisted of the transformation of certain of the fixed tissue cells into free macrophages which engulf and destroy the pneumococci much more effectively than do the neutrophils. The macrophages are dependent on opsonins for their antipneumococcic activity. The mechanism of recovery seemed to be of dual nature, consisting of a generalized process which acts to localize the infection and control or prevent bacteremia, and a local process which is the macrophage reaction whereby the lung is enabled to rid itself of the invading microorganisms. If both processes are effective, recovery results. If either one fails, death ensues. In experimental pneumonia, one attack conferred immunity to subsequent infection. This immunity lasted for months. The basis of such an immunity seemed to rest on the greatly accelerated macrophage reaction. After recovery a high degree of local immunity can be demonstrated in the involved lobes. It persists as long as the macrophages are present in the alveoli.

Andrews¹ made comparison of numerical with causative frequencies of types of pneumococcus which had been recovered from children with lobar pneumonia and separated them into 3 etiologic groups, the distribution of which, among patients with and without pneumonia and among other members of the same families, indicated a corresponding diversity in their etiologic significance. The A types appeared causative in all patients with lobar pneumonia from whom they were recovered.

They were associated with a relatively high incidence of pneumonia in infected persons, high mortality among infants, marked evidence of familial dissemination when the concurrent pneumonia was ascribed to these types and relatively low incidence in families without pneumonia or in those in which the patients did not show the same types of pneumococcus. Intermediate or B types appeared causative in many, but not all, of the children with lobar pneumonia from whom they were recovered. In comparison with the former group they showed a lower incidence of this disease in infected persons, lower mortality among infants, less evidence of familial dissemination when the concurrent pneumonia was ascribed to these types and a relatively high incidence in families without pneumonia or in those in which the patients had pneumonia ascribed to heterologous types. The least active types were listed as C types and appeared to be responsible for lobar pneumonia in few of the children from whom they were recovered. Evidence of their familial dissemination was uncommon, but these were the types most often recovered from persons coming in contact with patients whose pneumonia was ascribed to heterologous types.

Nemir, Andrews and Vinograd¹⁶ studied clinically and bacteriologically 1033 patients with pneumonia during four pneumonia seasons. In addition, they studied 425 patients having pneumococci in the respiratory passages but who did not have clinical pneumonia. They found most frequently pneumococci of Types I, VI, and XIV. These 3 types comprised 41.6 % of this series. They noted the age distribution of certain pneumococci. Type I was found rarely in patients under 2 years. On the other hand, Type XIX was cultured almost entirely from patients under this age. Types VI and XIV were more prevalent in infants and in the preschool group. Types XIX and VI occurred most frequently (30 %) in the patients who did not have pneumonia. Types I and XIV were rarely obtained from this group. Pneumococci of types III, VI and XIX were found almost as commonly in patients without pneumonia as in those with it. The pneumococci cultured from patients with bronchopneumonia were of the types commonly found in healthy carriers and in patients without pneumonia. The Type XIV pneumococcus was an exception, being present in 9.6 % of the patients with bronchopneumonia. Two-thirds of these patients had streptococci alone or in combination with the types of pneumococci found in common carriers.

Joppich^{12b} claimed that the Types I and II pneumococci must be regarded as the chief exciters of lobar pneumonia in the adult while all of the other types which he collectively groups as Type X cause focal pneumonia. In the infant and small child the dependency of the form of the pneumonia exciter is not so strict. It has been proved that certain infantile pneumonias with a cyclic course broken by a crisis and also real lobar pneumonia including forms with empyema in larger children are caused by Type X. This fact has been tentatively explained by a hypersensitivity of the infantile organism to the pneumococcus in general. In the light of this hypothesis, focal pneumonia would come under the normergic form and lobar pneumonia would come under the hyperergic form. In this way many of the features of the latter would seem to find an easier explanation. Bullova and

Greenbaum⁵ studied the age distribution and the mortality for the 32 types of the Cooper classification in 539 cases of pneumococcic pneumonias during a period from 1928 to 1934. During this time 1000 cases of pneumonia were observed in children brought to the Harlem Hospital. They said that some types of pneumococci which attack children are more important than others, and some types select children of certain ages for attack. The important types are I, VI, XIV, and XIX. They grouped their studies of type incidence to age by using the following age groups; from birth to 2 years, from birth to 6 years, from 2 years to puberty and from 6 years to puberty. They found the Type XIV the most frequently encountered type of pneumococcus. It was isolated in 83 (about 15.4%) of 539 cases. Type I was the next most frequent as it was seen in 79 cases or almost 15%. Type VI was observed in 10.2% of the group. Types IV, V, III, XIX and VII were seen in more than 3% of the cases in this order of incidence. In 70 cases, the "X" or unclassified type was observed and there were 15 cases of multiple infection or invasion by pneumococci and other organisms or by pneumococci of two types. When the patients were divided into those under 2 years of age and those over 2 years it was found that 262 (almost one-half) were infants under 2 and that 277 were between 2 and 12 years. The types of pneumococci causing pneumonia of infants under 2 years were distributed as follows: Type XIV caused 47 (17.9% of the cases); Type VI caused 34 (13%); Type XIX, 19 (7.3%) and Type I only 13 (5%). In 39 cases the organism was unclassified and there were 7 instances of multiple invasion. In the 277 cases in which the patient was over 2 years of age the dominant type was I. It was seen in 66 cases or almost 24%, which approaches the frequency of this type in adults. Type XIV was isolated in 36 cases (13%); Type V in 22 cases; Type VI in 21; Type IV in 17; Type III in 16 and Type VII in 12 cases. Types II, VIII and XIX were each observed in 6 cases and there were 8 cases of multiple invasion. The most important type of pneumococcus obtained from the infants under 2 years of age was Type XIV. After the age of 6 years it gave way in dominance to Type I. Type VI, which was important before the age of 6 years, was persistently so beyond that age period. Type XIX, which occurred frequently before the age of 2 years, was not seen after the age of 6. Type XVIII was noted chiefly before the age of 6. Types III, IV, V, and VII were seen equally distributed in children of all age groups. These observers found that some types of pneumococci caused fatal involvement more frequently than others. Some of the types designated by the higher numbers are infrequently isolated but cause a fatal outcome more often than do types which are commonly met. They found a very high death rate in the rare Types XVI, XVII and XXIII.

Fleming⁹ made leukocyte counts during the course of the disease in 147 cases of lobar pneumonia. He found the distribution according to types of pneumococcus as follows: 58 cases of Type I with 4 deaths; 51 cases of Type II with 10 deaths; 7 cases of Type III with 5 deaths and 31 cases of Group X with 2 deaths. He found that during the first 3 days of illness leukocytosis with a white cell count greater than 20,000 was characteristic of pneumonia due to Type I, while the

count in pneumonia due to Type II was usually below 20,000. The count in most cases of pneumonia due to Group X strains resembled those with Type I as the causative factor, while that in pneumonia due to Type III resembled the count in severe pneumonia due to Type II in which it was low. He found that the average daily counts in the various types of pneumonia showed separate levels during the early days of the illness. This makes it possible to make a differentiation of pneumonia due to Type II from that due to Type I and from that due to Group X strains. He used for prognostic purposes the leukocyte count in conjunction with the type of organism, the age of the patient and the duration of the illness.

In a discussion of the course of lobar pneumonia in children Ewstatiw⁸ said that the onset of pronounced lobar pneumonia in the child, contrary to that in adults, is often preceded by fatigue, nosebleed, headaches, vomiting, cough and other symptoms which cannot in good faith be considered as prodromal symptoms of pneumonia. As to the defervescence, it is seldom definitely critical. Often it is pseudocritical or preceded by one or several sharp drops in temperature before finally dropping to normal. In some cases, the subsidence of the temperature is definitely by lysis. He pointed out that pneumonia is a septic disease and stated that fever probably exists as long as there are exciters in the blood. The pneumonic focus is the expression of localization of the disease and as such is comparable to a pulmonary exanthema in the sense of Pirquet. The course of the disease in the child expresses this in a manner which indicates that the defense mechanism, especially the reticulo-endothelial system, is in an undeveloped condition. It has not had time nor opportunity to collect specific and non-specific immuno-biologic experience. In some children, the diagnosis may be difficult for some days. Savoye¹⁹ commented that there are cases of pneumonia in children in which the pathologic process shows no signs for several days after the onset of the disease but later gives typical signs. There are other cases in which the patients go through the entire course from onset to complete recovery without any demonstrable physical findings. From the roentgenologic point of view the pneumonia in these patients is not all central. Typical triangular shadows with bases at the peripheries of the lungs have been observed in which no signs were present. It is believed that physical signs are produced as the result of congestion about solid, hepatized areas. When the latter are present without the former, air cannot pass in and out of alveoli to produce blowing breathing and crepitations.

As a diagnostic and prognostic aid Brooks⁴ used a new method which he devised. He found that early in pneumonia there is a greatly accelerated blood sedimentation rate, which gradually returns to normal as the patient recovers. The normal curve does not occur until all signs obtained by roentgenologic and physical examination are normal. This indicates that the sedimentation rate is highly sensitive to a pathologic condition in the lungs. In cases of severe pneumonia in which the clinical condition progresses unfavorably the sedimentation is more abrupt and falls to still lower levels. This type of curve constitutes a bad prognostic omen.

Langley, Mackay and Stent¹³ examined the blood serum of patients

suffering from pneumonia for agglutinins. They also tested the effect of serum therapy on the occurrence of agglutinins. They found that agglutinins are recognizable in the serum of the patient with lobar pneumonia when the infection is due to organisms of Type I or II. These agglutinins are closely related to recovery as they are absent in cases in which the infection is fatal. After intravenous injection of 20,000 units each of concentrated Type I and Type II pneumococcus serum, agglutinins for the heterologous organisms are readily recognized in the patient's serum but may disappear with the injection of homologous serum. These authors suggested that the test for agglutinins is a reasonable means of determining the number of doses of serum required in any patient.

In the current literature are found other methods of treating pneumonia. One such method is discussed by Bolton³ who reported a series of patients, a number of whom he treated by administering stock vaccine. There were 168 patients with primary pneumonia and of these 91 were admitted within the first 3 days of the disease, and of these, the vaccine was given to 32. Vaccine treatment reduced the duration of the uncomplicated pneumonia by an average of 3 days. He found that recovery within 5 days of the development of the pneumonia was much more likely if the vaccine had been administered. Certain of the cases responded immediately to vaccine with a crisis and with marked improvement in the clinical condition in 12 hours. There seemed to be some risk in administering large doses of vaccine to patients who gave a history of chronic cough prior to the onset of the acute condition. In his series, the mortality was 13 of the 59 control patients who did not get vaccine treatment while only 6 of the 32 who received vaccine died.

Both statistical evidence and clinical observations of individuals in a large series of patients has convinced Nemir¹⁵ that Types I and XIV sera are valuable and effective aids in the treatment of pneumonia in children. In a smaller series, Types VII, V and II have been shown also to be valuable. Even though dramatic response to serum therapy may be obtained, other considerations are important before making the decision to use antipneumococcus serum in children. Since the mortality rate of lobar pneumonia is low in children more than 2 or 3 years of age, a specific therapeutic agent is not imperative. Treatment of patients with serum late in the disease is useless in patients less than 12 years as it has little effect on mortality and none on complications. A bacteremia, although discovered late, is usually helped by the use of serum and should be treated in this manner. This is a rare complication in children but when it is present it indicates very severe and overwhelming infection. The author recommended the use of homologous serum early in the disease in infants severely ill with Type XIV pneumococcus pneumonia. This is especially important because in the age group below 2 years the mortality rate is high. Indiscriminate use of serum for moderately or mildly ill patients is not advisable because of the sensitization to horse serum. With the production of satisfactory sera from rabbits this objection may be removed.

Harper¹¹ instituted artificial pneumothorax without fatality in the treatment of 22 children with lobar pneumonia. Their ages ranged from 15 months to 15 years. Most children required sedatives, and

for this purpose morphine gave excellent results. A rise in the interpleural pressure averaging +4 cm. of water was observed when patients who had been lying on their sides during the injection of air were turned to lie on their backs. Since the extent of the rise varied with the age and other factors, it seemed best to treat the children in the supine position. It must therefore be remembered in comparing these data with those of other authors that the readings of interpleural pressure are from 0 to +7 cm. of water higher than they would be if the patients had been lying on their sides, with the collapsed lungs upwards. In general, the results of compression on the pneumonic lung were encouraging when early and good collapse was obtained and were of doubtful value when compression was either delayed or incomplete. More complete and more rapid compression of the lung without discomfort to the patient was obtained by decreasing the rate of injection of air used in the early cases to a speed of from 7 to 9 cc. of air per minute, but at the same time increasing the amount of air especially on the initiation of pneumothorax. These observations suggested that the interpleural pressure required to give early and good collapse varied both with the age of the child and the extent of the pneumonic infiltration. Tentative levels of pressure were suggested which gave satisfactory results in children older than 6 years. The interpleural pressure was pushed slowly towards these tentative levels, with reliance on the symptomatology, especially beginning dyspnea and on evidence of mediastinal shift for warning to stop. In all cases in this series respiratory distress passed away within a few hours. At the first renewal of air, given after an interval of about 4 hours, the pressure was carried to higher levels without causing disturbing symptoms. The author stated that this work did not establish the value of artificial pneumothorax therapy in lobar pneumonia in children. A technique has been developed for the therapeutic use of this procedure, which when satisfactorily carried out, gave encouraging results. In evaluating the results it would be well to keep in mind that the technique developed as the work progressed and that future patients should benefit from the technical improvements.

Another contribution to the therapy of pneumonia was the use of blood transfusions. Arena² stated there is little ground for the belief that the circulation will be embarrassed by transfusion at a time when the total circulating volume of blood is decreased. In the past 3 years he made efforts to give one or more transfusions to all infants and children on his service that had severe primary pneumonia, whether or not they had anemia. Because of the difficulty of securing donors 35 of these patients did not receive blood and consequently served as controls. The other 24 had one or more transfusions of citrated blood by the gravity method with a maximal amount of 20 cc. per kilo of body weight. The clinical symptoms, hemoglobin content and red and white cell counts for the two groups were almost identical. The only difference was that in the group who received transfusions there were probably more ill patients and more infants so that the expectations in this group were worse. However, prompt and marked improvement usually followed the transfusion, and the patient appeared more comfortable. The temperature fell by crisis in 24 hours of the transfusion

in 15 patients and in 48 hours in the other 9. The average interval between the onset of the disease and the crisis or lysis for this group was $7\frac{9}{10}$ days. Four of these children had the complication of suppurative otitis media and 1 died. For the 35 patients who did not receive transfusions the average interval between onset and the crisis or lysis was $9\frac{9}{10}$ days. Of these children, 3 had the complication of empyema, 9 had otitis media and 5 died. The severe dyspnea and cyanosis, which many of these children had, were improved instead of made worse by the transfusion. No circulatory embarrassment was noted during or after the procedure. After the transfusion several of the patients had an immediate rise in temperature, which was usually followed by an immediate crisis. The explanation of the beneficial effect of the blood transfusion is not known. It seems doubtful that the correction of anemia could be a factor. The results were as good in the patients with severe anemia as in those with moderate anemia. Apparently the only contraindication for transfusion in children is damage to the kidneys.

Degwitz⁶ discussed the mortality rate in 2 groups of children who had bronchopneumonia. The first group comprised 334 which were treated during the time the fresh air treatment was not yet used. In the second group of 424 children, the fresh air treatment was used. The ages of the children, the percentage of severe cases and the incidence of complications were about the same in the two groups. Certain indispensable nursing and medicinal measures were about the same for the two groups. The first group was treated in ordinary wards while the second group received fresh air treatment in open-air verandas or in open-air rooms. A comparison of the mortality rates in the two groups proved that in the open-air group there were only one-third of the deaths that occurred in the other group. It would seem, therefore, that there was a distinct advantage in this method of treatment.

The use of sulphanilamide in the treatment of pneumonia has been discussed at some length in the literature. Its value in children is as great as its value in adults especially in cases in which specific type serum cannot be employed. The limitations of space do not permit discussion of this valuable treatment which deserves consideration by itself.

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PHYSIOLOGY

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The Occurrence of Chemotaxis in the Slime Mold. DALE REX CO-MAN (Laboratory of Pathology, University of Pennsylvania). Investigations of chemotaxis in polymorphonuclear leukocytes have left unanswered certain fundamental questions. To understand chemotaxis we should know something about the nature of substances which cause it, the organisms or cells which show it, and the mechanism concerned.

In the hope of obtaining such information, we sought an organism of a relatively low order of life, in contrast to highly specialized cells, and one which could be adapted to both gross and microscopic study. The slime mold, *Physarum polycephalum*, was chosen and a culture of this organism was obtained from Professor Seifriz of the Botany Department. The mold grows over a moist surface in soft yellow strands and masses. Microscopically, it appears as a syncytium of granular protoplasm which shows rhythmic streaming.

In gross experiments, the mold, growing on agar plates, was repelled by hydrogen and hydroxyl ions, was attracted by dextrose, and was indifferent to sucrose and sodium chloride. It was also indifferent to crystalline egg albumen and insulin. Fifteen to 20 plates were used for each substance tested, and the same result was obtained in all the plates.

In microscopic experiments, a piece of the mold was attracted by one substance and then caused to reverse its direction of locomotion by introducing a repelling substance. Evidence obtained from such experiments throws doubt on the surface tension theory of chemotaxis and suggests the probability that the organism reacts to a stimulus transmitted throughout its substance.

Persistent Diabetes Following Injections of Anterior Pituitary Extract. F. C. DOHAN, and F. D. W. LUKENS (George S. Cox Medical Research Institute, University of Pennsylvania). F. G. Young (Lancet, 2, 372, 1937), has recently reported the production in dogs of diabetes which continued for months after the cessation of daily intraperitoneal injections of increasingly larger doses of anterior pituitary extract. Using the technique described by Young, we have produced an apparently permanent diabetes in 3 of 8 dogs after the several weeks during which injections were given. During this period, there was a marked hypoglycemia and glycosuria. The severity of the postinjection diabetes varied with the individual dogs. Two dogs excreted glucose approximately equal in amount to the available carbohydrate in their food. During fasting or fat feeding there was very slight glycosuria or ketonuria—much less than that of the depancreatized dog. The responses to diets, glucose tolerance tests and insulin tests were reported. Island lesions were noted in one animal suitable for this observation (in press, Am. J. Physiol.).

The Action of Insulin Upon Protein and Carbohydrate Metabolism of Surviving Liver Slices of Normal and Diabetic Animals. W. C. STADIE, F. D. W. LUKENS, and J. A. ZAPP (Laboratory of Research Medicine and the Cox Institute, University of Pennsylvania). Experiments were made on surviving liver slices equilibrated in phosphate buffer for 2 hours at 38° C. Oxygen consumption, the respiratory quotient, the total fermentable carbohydrate, and the urea formation were measured. Various amino acids were used as nutrients and the effect of insulin in the medium upon the above noted metabolites was measured. The tissues used were from normal rats, normal cats, diabetic cats, hypophysectomized cats, "Houssay" cats, and cats made diabetic by the injection of anterior pituitary extracts.

The following summarizes the findings: (1) In the normal rat or cat we have been unable to find significant inhibition of urea formation by insulin when the medium contains no added nutrient. In the same circumstances, we have been unable to demonstrate any inhibition of urea formation in the diabetic cat liver. (2) With *dl*-alanine in the medium we have found with considerable regularity in the normal rat and cat that insulin produces an inhibition of 10 to 15% of the extra urea formation which *dl*-alanine produces. In the diabetic cat, we have found essentially the same thing. However, the insulin effect is not greater than that found in normals. (3) Insulin has no inhibitory action on the urea formation owing to the presence of the naturally occurring amino acids. With the non-natural amino acids there is found quite regularly an inhibition of urea formation by insulin. (4) Injection of anterior pituitary extracts sometimes causes marked increase of the deaminating power of the liver. Insulin inhibits markedly this enhanced urea formation, but the effects are inconstant. (5) No effects of insulin upon carbohydrate synthesis by the liver have been observed in normal rats, cats, or diabetic cats.

Transient Ventricular Fibrillation in Man. WILLIAM G. LEAMAN (Department of Cardiology, Woman's Medical College of Pennsylvania). Transient ventricular fibrillation is demonstrated in an electrocardiogram from a patient, aged 76, suffering from hypertensive cardiovascular disease and presenting varying grades of *A-V* block. During a typical Adams-Stokes seizure the tracing showed, in addition to other arrhythmias, a period of ventricular fibrillation lasting 42 seconds. Recovery occurred through the development of an idioventricular rhythm with ultimate reestablishment of a 2 to 1 heart block (auricular rate 80, ventricular rate 40). The patient left the hospital in fairly good condition. However, ventricular fibrillation, as viewed by the physiologist in the larger, intact laboratory animal, is nearly always an irreversible state produced by the manipulation of the heart, electrical stimuli, occlusion of the coronary arteries, heating, alteration in vagal or sympathetic tone, and the toxic action of certain drugs. For this reason, cases demonstrating the mechanism with recovery in man should always be carefully studied. The number reported in literature is small (18 instances). Nearly all patients had advanced heart disease with associated complete *A-V* block and Adams-Stokes syndrome. There is still considerable controversy in regard to the electrocardiographic diagnosis

of ventricular fibrillation in man. We believe it can be diagnosed when the waves present the extremely bizarre appearance seen in the motion picture film of this tracing with total irregularity of rate and rhythm of the type obtained when the lack of coördinated contraction of ventricular fibrillation is actually observed in the exposed dog heart. We conclude from a study of the record of this case, and of a similar one from our own laboratory, in a man of 66 suffering from the same type of heart disease that, in man, ventricular fibrillation can be a reversible process with complete recovery possible, and that such occurrences are more frequent than the scant number of reports in the literature tend to indicate.

CORRECTION.—In Dr. Schipdt's article on "Observations on Blood Regeneration in Man," the footnote on p. 639 of the November, 1938, number should read: "In 17 patients" instead of "77 patients."

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ORIGINAL ARTICLES.

THE ALLEGED DULLNESS OVER THE APEX OF THE NORMAL
RIGHT LUNG.*

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(From the Department of Medicine.)

ALL textbooks on Physical Diagnosis that I have consulted state that the percussion notes over the apex of the normal right lung are of higher pitch than those over corresponding areas on the left side. Some authors describe the note in the right suprascapular region, especially, as dull, and warn the examiner against mistaking the difference in pitch for evidence of early tuberculosis. Various explanations have been offered for the alleged higher pitch on the right side, such as the position of the eparterial bronchus, the proximity of the right apex to the trachea and the greater development of the shoulder muscles in right-handed persons.

For years I accepted the statements in the textbooks unquestioningly. But when I attempted to demonstrate to students a higher pitch in the right suprascapular region than in the left, the exceptions were so numerous that a reinvestigation of the subject seemed desirable. Second year students† (232 men and 8 women) taking the course on the physical signs of the normal chest, in which they served as subjects for each other, furnished the material for this study. In view of the wide divergence of the results obtained from the prevailing belief that the higher pitch is on the right side, the method of conducting the examinations will be described. In order to avoid variations in technique, I examined personally as many of

* Read by title before the Association of American Physicians, May, 1929 (Abstr. Trans. Assn. Am. Phys., 44, 322, 1929).

† New York University College of Medicine.

the subjects as possible, roughly some 75%, and all doubtful or disputed cases; and to reduce any error that might arise from the fallibility of the ear in comparing the pitch on the two sides, the "collective" ear of the section was employed; that is, the note was sounded and the student-group (averaging 10) was asked to locate its pitch. In case of disagreement, the percussion was repeated until unanimity was reached or the preponderant opinion was accepted as correct.

Of 223 students, the higher pitch was found on the left side in 158 (70.85%) and on the right side in 65 (29.10%). The pitch was found to be the same on both sides in 8 students and was variable on different occasions in 2 students. The records of 7 students are missing. In 77 students the percussion notes in the right and left supraclavicular and infraclavicular regions were compared with each other and with the note in the suprascapular region. In all but 10 instances, the pitch of the notes in the supraclavicular and the infraclavicular regions corresponded with the pitch in the suprascapular region on the corresponding side.

The results of this study have led me to seek an explanation of the current statement that the pitch of the percussion note over the right apex is higher than that over the left. As stated above, among the reasons usually assigned are the position of the eparterial bronchus and the proximity of the right apex to the trachea. If the eparterial bronchus and trachea have any influence on the percussion note, it is difficult to understand why they would not lower its pitch instead of raising it: if the vibrations reach them, their frequencies should be lessened by the larger air spaces and the pitch of the sound lowered. The tympany found in some cases of pneumonia at certain stages, where the bronchi definitely modify the pitch of the note, lends support to this view. And such an assumption would explain the statistical preponderance of the lower pitch on the right side in this study.

Another reason assigned for the higher pitch on the right side is the greater development of the muscles of the right shoulder in right-handed persons. The thickness and physical state of the structures overlying an area of lung undoubtedly do affect the pitch of the note, for example, over a rib and in an intercostal space. And if care is not taken to damp the vibrations in the thicker muscles of the right suprascapular region, the percussion note will have a higher pitch. But it is easily possible to reduce the vibrations in the muscles to a minimum and obtain the pure pulmonary note. This phase of the subject will be referred to later on.

It may be pointed out that no author reports any statistical studies of the question on normal persons.

Technique of Percussion. Percussion, in my opinion, is the greatest of the arts employed in making a physical examination. Percussion often gives the first clue to the existence of a lesion. It is

capable of disclosing lesions that are difficult to detect by other means, even Roentgen rays, such as localized thickenings of the pleura. To become adept in percussion requires long training. And I am convinced that such training should be conducted by the older and more experienced members of teaching staffs.

So many excellent discussions of the technique of percussion have been written that I hesitate to add another. But since I have made a special study of the subject for many years, it may be that some points in the technique I have come to rely on may be suggestive to others. The discussion will be discursive rather than systematic. The fingers are the only instruments the physician needs for percussion and are the best. Artificial plexors and pleximeters introduce adventitious sounds and make interpretation more difficult. In addition, they completely deprive the examiner of the information he may obtain through the vibration sense—the “feel” of the area percussed. The index finger of the left hand should be used as the pleximeter as it is under easier control than the middle finger. The use of crossed fingers as a pleximeter or the so-called orthopercussion (the pleximeter flexed to a right angle at the 2d phalanx) unnecessarily complicates the procedure and lessens the acuity of perception. The pleximeter should be applied with pressure. The amount of pressure required varies greatly in different persons and in different regions of the same chest. When the chest-wall is thin, the pleximeter need only be placed firmly on the surface; when the chest-wall is thick, and over the scapulæ, much pressure is required, so much in fact that the finger may feel sore after a prolonged demonstration. The object of the pressure is to damp the vibrations in the overlying structures so that the pulmonary note may be obtained in its purest form. It is always advisable to vary the pressure until the observer is satisfied that he is obtaining the note characteristic for the region or for a pathologic lesion. The overlying muscles should be relaxed, especially when delicate shades of pitch have to be evaluated. For example, when comparing the supraclavicular regions, the patient should look straight ahead. If the face is turned to one side, the stretching of the platysma on the opposite side will raise the pitch of the note just as hunching a shoulder raises the pitch of the percussion note over the suprascapular region.

The middle finger of the right hand should be used as the plexor—it is on the central axis of the forearm and hand. The use of two or more fingers is never necessary even in the heaviest percussion and is likely to alter the pitch and distort quality of the sound. The blow should be delivered on the middle phalanx of the pleximeter with the pulp of the finger used as the plexor—striking on the nail or first joint introduces confusion vibrations. The power for the blow is derived from flexing the finger, on the knuckle as a fulcrum, and from the wrist. In the lightest percussion all necessary power

may be derived from the finger alone. Preliminary extension of the wrist facilitates the execution of the movement and preserves the arc through which the end of the plexor must travel in order to lessen the chance of injuring the pleximeter with the nail of the plexor—an important consideration in prolonged percussion. When additional power is desired, the wrist may be sharply flexed. Another method is to fix the wrist and to obtain what additional power is required from the forearm. This method is not recommended until percussing from the knuckle and wrist has become a settled habit.

As the stroke is delivered by the middle finger, the other fingers automatically extend in a compensatory movement. In view of the frequency with which it has been stated that the plexor must be lifted quickly from the pleximeter after striking the blow to prevent damping of the vibrations, for years I have experimented on the subject. Neither I nor the participants in the experiments have been able to detect any variation in the sound or the "feel" of the area when the plexor was allowed to remain lightly on the pleximeter. And I have found that the mental and physical effort required to lift the plexor quickly interfered with concentration on the sound elicited.

The strength of the stroke of the plexor must be adjusted to the local necessities. The rule should be to use the least force possible. The object is to obtain the note of the lung with the least interference from vibrations in the overlying or nearby structures. When the stroke is too hard reverberations alter the quality of the sound. It is rarely possible to obtain the optimum note with the first stroke of the plexor. The force of the blow must be adjusted not only to the thickness of the overlying structures but to the degree of pressure by the pleximeter—there is always an optimum for each of them—to obtain the purest note. This requires an attentive ear and knowledge of many chests both in health and disease.

Palpatory Percussion. The term palpatory percussion has been given several interpretations. I shall use it to mean palpation of the vibrations set in motion by percussion. The percussion may be mediate or immediate. Both procedures are based on the ability of the examiner to perceive vibrations through his fingers and both are susceptible of a high degree of cultivation. My personal preference is for mediate percussion where both pleximeter and plexor participate in the sensations.

The technique of palpatory percussion is similar to that described for audible percussion. The same fingers are used as plexor and pleximeter. The pleximeter is applied with a minimum of pressure—some pressure is required to damp the vibrations set up in the finger itself. This can easily be demonstrated on a desk- or table-top, for example. The blow from the plexor must be so light as to produce little or no sound. Sometimes, however, it is desirable to compare the frequencies of the vibrations with both the finger and the ear.

Strong pressure and a heavy blow blunt the vibration sense. In palpatory percussion the frequencies of the vibrations in adjacent regions are compared by the finger instead of by the ear.

In my contacts with other physicians, the use of palpatory percussion has been most frequently observed in the technique of older practitioners. They evidently had come to rely more on the "feel" of the area than on the sound elicited. And their diagnoses usually were correct. Personally, without conscious intent, I have come to use palpatory percussion more and more, especially in outlining the heart, but in most examinations I employ both methods. Palpatory percussion is likewise useful in locating the lower edge of the liver and demonstrating enlargement of the spleen, when it is difficult to palpate.

In my opinion, the value of palpatory percussion has not been sufficiently emphasized in textbooks. I would suggest that students and younger practitioners cultivate the vibration sense. Palpatory percussion of table-tops, doors, window-panes and frames, will reveal how acute the vibration sense is and how useful it may become in physical examination.

Summary. 1. Textbooks on Physical Diagnosis assert that on percussion a higher pitch is obtained over the right suprascapular region than over the left.

2. In this study of the percussion notes over the apices of the lungs of 223 normal second-year medical students, the higher pitch was found over the left apex in 158 (70.85%) and over the right apex in 65 (29.10%) of the students.

3. It is suggested that the preponderance of the lower pitch on the right side is due to the position of the eparterial bronchus and to the proximity of the right apex of the lung to the trachea.

4. The author's techniques of audible and palpatory percussion are described and the suggestion is made that the "feel" or "resistance" of a region is an expression of the vibration sense.

In conclusion I wish to express my appreciation and thanks to Doctors John E. Sawhill, William B. Rawls, Robert P. Wallace, Hannibal DeBellis, Louis L. Shapiro, and Max P. Cowett, formerly my assistants, for their help in obtaining the data on which this communication is based.

THE RÔLE OF THE VIBRATION SENSE IN PERCUSSION.*

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VIBRATIONS are the chief media through which all animals, from ameba to man, receive information concerning their environment and the changes occurring in it. These vibrations vary enormously

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in frequency, from ultra-violet light to the coarse jars, not affecting posture or equilibration, that may be perceived by any part of or the whole body.

According to Jennings,⁹ the naked protoplasm of ameba responds to all classes of stimuli to which any animal responds, including light and mechanical jars. But in the process of evolution to higher orders special receptors have been developed by animals to sift out vibrations within more or less definite ranges of frequency. Some insects have sound-producing mechanisms and tympanal organs and are believed to "hear." In the experiments of Wever and Bray,²⁰ a cricket responded to vibrations of 250 to 11,000 cycles per second and a katydid to vibrations of 800 to 45,000 cycles per second. Cole¹ concluded from his experiments on the common fresh water flea that the first antennæ are receptors for sound waves. Sound waves in air, even when produced by naval guns (Parker^{13b}), quickly spend themselves in water, and fishes have been denied the sense of hearing. But the experiments of Parker,^{13a} of Manning¹¹ and others indicate that fish do hear sounds produced in water, in fact, some fish have developed elaborate systems for the detection of such vibrations in which the skin, the lateral-line and the ear participate. Manning found that goldfish responded to vibrations, produced by a submerged telephone receiver, of from 43 to 2752 cycles per second, with the upper limit for the ear undetermined. Vibrations as slow as 6 per second may also be perceived by the lateral-line. There is evidence that in some fishes the swimming-bladder relays sound waves to the Weberian ossicles and the ear (Evans).⁴

The eyes of man respond to vibrations of 400,000 to 800,000 billions per second; the ears of man respond to vibrations of some 30 to 30,000 vibrations per second (Herrick).⁸ In addition to the eyes and ears, less elaborate receptors have been evolved, in man at least, for the detection of vibrations of other frequencies which strike or penetrate the skin, such as infrared rays. Yet the fact that individual cells of the skin react to sunlight, as illustrated by the deposition of melanin, leaves no doubt that they have not lost the primordial function of unicellular organisms individually to perceive vibrations. The vibrations referred to above constitute only small fractions of the total range of vibrations. Roughly speaking, they lie at opposite ends of the scale of frequencies. Wood and Loomis²¹ found that supersonic waves with frequencies of 300,000 to 500,000 per second, of great intensity, destroy protoplasm. But very little is known about the effects of vibrations of other intermediate frequencies upon animal life.

Surprisingly little study has been devoted to the vibration sense in man as a sense function. In physiologies the subject is dismissed with a few lines or paragraphs. Numerous clinical studies have been undertaken chiefly to determine the effects upon the vibration sense of injuries and diseases of the peripheral and central nervous systems

and the pathways of the sensation to the brain. In some of these studies the observations have been extended to include normal persons. Many facts of physiologic and diagnostic significance have been discovered. The tests were carried out for most part with the aid of tuning-forks of different frequencies: in addition, Tilney¹⁸ used the pallesthesiometer* and blasts from a loud speaker. The tuning forks usually were placed over bones and bony eminences, in some instances over soft parts, and held in position until the fork "ran down." It is obvious that these procedures only partially reproduce the conditions of actual life with respect to the propagation, transmission and reception of the vibrations which the body is able to perceive.

The most complete study of the vibration sense in the literature is by Helen Keller.¹⁰ This study fulfills all the criteria of scientific investigation, an unprejudiced mind, repetition of experiment and adequate controls, and is entitled to scientific rating. Miss Keller surely had no theories to prove, her observations have been repeated daily throughout the greater part of her life, and her controls have been human experience. The fact that the study is purely qualitative in no way detracts from its scientific character—it merely opens up another field of inquiry. A knowledge of the physics of sound may satisfy intellectual curiosity but adds nothing to the usefulness of the vibration sense to the individual—or to the enjoyment of grand opera. As has been pointed out, no other student of the vibration sense has duplicated the conditions of actual life in his experiments. The surface area exposed to the vibrations of a tuning-fork is limited to the size of its foot. In Miss Keller's experiments the surface exposed has varied from the finger-tips to apparently the whole body. The tuning-forks have been standardized for the most part to definite frequencies, though in some experiments a number of forks of different frequencies have been used. Miss Keller's observations have included all frequencies that her vibration sense is capable of receiving.

The vibration sense has played the chief rôle among the senses in orienting Miss Keller to her environment. Her observations bear so directly upon the rôle of the vibration sense in percussion that extensive quotations from her report seem desirable. It may be pointed out here that, contrary to what might have been expected, Tilney found Miss Keller's vibration sense no keener than that of the average normal person. When not handicapped by loss of sight and hearing, the individual finds little use for the vibration sense and usually ignores its messages—and possibilities.

Miss Keller states, "I derive much knowledge of every-day matters from the jars and the jolts which are to be felt everywhere in the house. . . . Footsteps vary tactually according to the age, sex, and the manners of the walker. . . . Often footsteps reveal in

* Rydel and Seiffer suggested the term pallesthesia for the vibration sense.

some measure the character and mood of the walker. . . . When a carpenter works in the house or in the barn near by, I know by the slanting, up and down, toothed vibration and the ringing concussion of blow upon blow, that he is sawing or hammering. . . . By placing my hand on a person's lips and throat, I gain an idea of many specific vibrations and interpret them: a boy's chuckle . . . the moan of pain, a whisper . . . a sob . . . a gasp. . . . I have heard the tiger talk by putting my hand on the bars of his cage. . . . There are tactual vibrations that do not belong to skin-touch. They penetrate the skin, the nerves, the bones, like pain, heat and cold. The beat of a drum smites me through from the chest to the shoulder-blades. . . . I listen with awe to the roll of thunder. . . . Fog-whistles are my vibratory nightmares. . . . Every atom of my body is a vibrascope."

There has been much discussion concerning the nature of the vibration sense and how it is mediated. Rumpf,¹⁵ the first to study it quantitatively, concluded that the sensation is transmitted by the cutaneous nerves, like heat, cold, pressure. Treitel¹⁹ thought it distinct from the sense of touch. Egger³ suggested the term "*la sensibilité osseuse*" for the vibration sense because he considered the periosteum, ligaments, and capsules of joints the anatomical basis of the sensation. Symns¹⁷ considered the vibration sense distinct from pain and temperature; that it is a mixed sensation closely allied to deep sensibility. According to von Frey,⁵ the vibration sense is a function of the skin, with the bones acting as resonators. Gray⁶ agrees that vibrations are best perceived through the medium of bones but that it is not necessarily an osseous sensation. In the opinion of Rydel and Seiffer¹⁶ the vibration sense is a special form of sensation, distinct from touch and pressure, a function of deep sensibility, and that all superposed tissues take part in its perception. Tilney has shown that the skin and soft tissues of the webs between the fingers and folds of loose skin picked up by the thumb and finger are sensitive to vibrations. My observations in percussing solid internal organs, such as the heart, liver, and so on, confirm the view that the vibration sense is independent of the senses of touch and pressure. In delimiting the left border of the heart by palpatory percussion, from left to right in the fifth left intercostal space, the subject detects the change in wave-length when the heart is reached as quickly as does the observer. In this case, the vibrations set in motion by the blow must travel through the chest-wall and a layer of lung to the heart and be reflected back to the pleximeter finger, and the intervention of either touch- or pressure-sense is clearly eliminated. Different subjects have described the sensation when the heart is reached as a slight "shock" or "jar" felt within the chest.

In my opinion, the most significant conclusion reached by any investigator of the vibration sense is Miss Keller's: "every atom

of my body is a vibrascope." This is in agreement with Jennings' statement that the nervous system and sense organs are not necessary for the reception of any particular class of stimuli. All biologists agree that every living cell in the human body retains some of the functions possessed by protozoa; for example, all breathe and carry on their metabolic exchanges, however much these may have been modified. Many cells specialize in a definite function and have completely lost one or more of the others: muscle cells contract but cannot reproduce themselves. On the basis of these considerations and the fact that, during percussion, changes in the frequencies of vibration waves are detected by the heart, the liver, the spleen and that portion of a lung consolidated by pneumonia, I would suggest that the vibration sense is a special sense, mediated by the cells themselves instead of by specialized receptors like those for touch; in other words, the vibration sense is a survival of the sensitivity of protozoa to the coarser vibrations and is retained by all living cells of the body in greater or less degree. If this theory is correct, the vibration sense is independent of the senses of touch, pressure, pain, temperature and deep sensibility.

With this background it is easier to understand the rôle of the vibration sense in percussion. For years it has been recognized that the sound produced during percussion is only one of the elements entering into the interpretation of the results: the other is the way the object "feels." This has been described also as the "sense of resistance" and much significance has always been attached to it. Piorry,¹⁴ who introduced mediate percussion, discussed it. Ebstein² published a monograph on *Tastperkussion*. Norris and Landis¹² say that a physician is able to state positively whether a given note is resonant or flat, with his ears closed, simply by his sense of touch; they add that "our judgments are derived from the pressure sense of the skin and the muscle sense." Many other authors have referred to the sensations imparted to the fingers (both pleximeter and plexor) during the act of percussion. But nowhere in the literature, after an extended search, have I been able to find any reference to the relation between the "feel" or resistance of an organ or area and the vibration sense. The vibration sense is in fact a sixth sense that the physician brings, consciously or unconsciously, into the interpretation of physical signs. Laura Bridgman⁷ asserted that she "heard" with her feet. Miss Keller "hears" the human voice by placing her fingers on the speaker's lips and throat. In palpation of the chest, as well as in percussion, the physician "hears" with his hand or his fingers.

The vibration sense, it should be pointed out, is capable only of comparing the frequencies of vibrations, not of measuring them. But just as some persons possess the ability of locating on the scale with a fair degree of accuracy the pitch of a sound, so, I believe, clinicians may acquire the ability to recognize through the vibra-

tion sense an abnormal "pitch" on percussion before they compare it with adjacent normal areas. Pitch is translated by the vibration sense into "feel" or resistance. Areas that give a high-pitched sound on percussion "feel" hard or resistant: areas giving sounds of lower pitch "feel" softer. The acuity of the vibration sense was appreciated by Piorry, who stated that the finger that strikes gives as accurate information as the ear that hears. My experience, including the frequent comparison of sound with the sensation in the pleximeter finger in mediate percussion and in the plexor in immediate, is in complete agreement with this conclusion of Piorry.

If I may judge by my observations, years of training are required—self-training for the most part—to understand the true significance of the "feel" or resistance of a region—the sound produced in percussion is emphasized to such an extent. It is easy enough to recognize that a pleural effusion or a lung consolidated by cancer "feels" hard, but the finer distinctions are often overlooked. "Feel" or resistance became clear to me only when I began to estimate it in terms of vibrations and the vibration sense. As I have watched older and more experienced physicians examine patients with apparently unorthodox methods of percussion, I was formerly inclined to be critical, yet I marveled at the accuracy of their diagnoses. In retrospect I doubt whether they themselves realized they were obtaining their information through a special sense. Looking on, I did not know what they were doing. The very fact that experience gradually leads to increased reliance upon the "feel" in percussion gives it special significance and indicates the importance of teaching students percussion in terms of vibrations and the vibration sense as well as in terms of sound.

In concluding this discussion, it may be pointed out that the vibration sense plays a rôle in auscultation only second to that in percussion. The best known illustration of this fact is the occasional case of aortic regurgitation in which the murmur cannot be heard with a stethoscope but is clearly audible when the ear is placed upon the chest, preferably upon the bare skin. Less striking instances occur constantly. My attitude is that it is always necessary in difficult cases to employ immediate auscultation, and that, to acquire familiarity with it, its frequent use is desirable. In immediate auscultation the tissues of the head, including the skin and bones, pick up the vibrations.

Summary. 1. The importance of vibrations in the orientation of animals to their environment is pointed out and studies on the reception of vibrations of different frequencies by certain lower animals are briefly reviewed.

2. Various studies of the vibration sense in man are reviewed, and a new concept of the nature of the vibration sense and how it is mediated, based on experiments in percussion, is presented. According to this theory, the vibration sense is a survival of the sensitivity

of protozoa to the coarser vibrations and is distinct from the senses of touch, pressure, pain, temperature and deep sensibility.

3. The relation of the vibration sense to interpretation of the results of percussion, especially palpatory percussion, is then discussed.

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SPECIFIC TREATMENT OF PNEUMOCOCCUS TYPE I PNEUMONIA.

INCLUDING THE USE OF HORSE AND RABBIT ANTIPNEUMOCOCCUS SERUMS AND SULPHANILAMIDE.

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THERE has been an unusual increase in interest recently in the methods and results of specific serum treatment of the pneumonias. It is appropriate at this time, therefore, to bring up to date the experience at the Boston City Hospital with the pneumonias due to the more frequent types of pneumococci to which this mode of therapy has been applied. The relative increase in the number of

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cases treated with serum at the hospital and the introduction, during the past year, of antipneumococcus rabbit serum and of sulphanilamide are further reasons for taking stock at this time. The present paper will deal with the cases of Type I pneumonia in adults. Those due to pneumococci of the other common types will be considered in separate communications. We shall consider in detail only the results obtained from 1935 to 1938, the three years that have elapsed since the last report.^{7c}

Patients, Materials and Methods. During the past few years, an effort has been made at this hospital to identify the common significant bacterial agents in all adult cases of acute pulmonary infection and also to type every pneumococcus encountered in these or other conditions. Between Sept., 1929, and July, 1938, the Type I pneumococcus was identified in 1125 cases. Table 1 shows the close association of this type with primary lobar pneumonia. Only 57 (5.1%) of all cases harboring Type I pneumococci did not have pneumonia or empyema. In only 14 instances (1.2%) was this organism obtained from the sputum or pharyngeal culture in the absence of pneumonia or empyema. Among the 897 cases of Type I pneumonia in adults, only 34 (3.8%) showed patchy or "atypical" pulmonary consolidation and in many of these the pneumonia was first recognized or the pneumococcus was first typed from autopsy material. More than 80% of these were "secondary," that is, followed injuries or operations or occurred during the course of other serious acute illness or during the end stages of severe chronic diseases. The remaining 863 cases showed typical lobar pneumonia according to the best evidence obtainable from autopsy, roentgenographic or physical findings. Among the latter, less than 7% were secondary.^{7a,18b}

TABLE 1.—PATIENTS HARBORING TYPE I PNEUMOCOCCI, 1929-1938.

Adults with lobar pneumonia	863
Adults with atypical pneumonia	34
Adults admitted with empyema	27
Infants and children* with pneumonia and/or empyema	144
Focal infections without pneumonia	43
Carriers or respiratory infections without pneumonia	14
Total number of cases	1125

* Not studied routinely. These types usually obtained from cultures of blood or pleural fluids.

Selection of Cases. During the earlier studies an attempt was made to treat alternate cases with specific serum either as they were encountered^{7b} or as the type was determined.^{20a} These methods of choosing cases proved to be neither desirable nor workable. It was then deemed best to treat with serum only those patients in whom the type was obtained early in the disease, 96 hours after the onset being chosen, on the basis of previous experience, as the dividing line. However, this was not adhered to very rigidly. As greater supplies of serum became available, this limit was gradually extended until all patients with Type I pneumococcus pneumonia were treated with serum as soon as this type was determined, except: 1, patients already showing evidence of recovery; 2, those in whom focal complications were already established; 3, patients in "collapse" with evidence of circulatory failure or pulmonary edema; and 4, certain doubtful cases in which it was shown that Type I agglutinins were present in the blood or when the immediate skin reaction to Type I specific capsular poly-

saccharide was positive.²¹ Some of the patients with focal complications were given serum, however, if the blood culture was positive or if the pneumonia was considered to be still active. Likewise, some of those in "shock" were treated after the "collapse" or pulmonary edema showed evidence of improvement under appropriate measures. Experimental lots of serum were used first to treat younger patients or those who were in good general condition unless no other serums were available at the time.

Serums Used. Some 80 different lots of concentrated antipneumococcus horse serum were used during the last 3 years. These ranged in potency from 1500 to 4500 units per cc.; 15 lots contained less than 2000, 34 contained from 2000 to 3000, and 31 had more than 3000 units per cc. Most of these lots were furnished for clinical trial before they were released for general use, and experimental methods were employed in the concentration of a number of them. Concentrated rabbit serums of five different lots were used, one with 10,000, three with 4500 and one with 1000 units per cc. Several different methods were used in the concentration of these serums. Except for occasional experimental lots, all Type I serums were standardized by the approved National Institute of Health mouse tests in relation to the control serum P11, to which a value of 300 Type I units per cc. was assigned.^{6,11} All the rabbit serums and 8 of the horse serums were monovalent. The rest were bivalent and contained Type II antibody. The concentration of the latter in terms of a similar standard unit (P11 = 150 Type II units) was from one-third to the same number of units as Type I. In the text and tables, numbers of units will refer to the actual titrated values in contrast to the values finally placed on the labels, which were usually from 10 to 40% less.

Typing. The Neufeld method^{15,19} applied directly to the sputum has been relied on to the largest extent for the original typing upon which therapy was based. In almost every instance this was checked by typing from the peritoneal exudate or heart's blood of a mouse inoculated with the sputum and/or from typical colonies picked off the surface of blood agar plates inoculated with the sputum or with the mouse's exudate or heart's blood. Typing from these materials was done either by macroscopic or microscopic agglutination or by the Neufeld method or by a combination of these methods. The direct sputum typing proved highly efficient. During this last 3-year period, a diagnosis of Type I by this method proved to be wrong, as judged by the results of mouse inoculation of the same material, in only 2% of the sputum specimens. Among the sputa which were examined by both the direct method and by mouse inoculation and which yielded Type I pneumococci from the mouse, this organism was not recognized directly in the sputum in 7% of the specimens. Patients from whom sputum was not obtainable were successfully typed, in most instances, by inoculating pharyngeal swabs into suitable broth containing defibrinated rabbits' blood, incubating for 4 to 6 hours, injecting some of the culture into a mouse and withdrawing peritoneal exudate from the mouse after 3 to 6 hours. Frequently, the broth culture yielded the type directly. Blood cultures were taken frequently during the acute disease and positive cultures were typed directly by the Neufeld or by agglutination methods.

Serum Injections and Dosage. All of the serums were given intravenously except in occasional cases where intramuscular injections were used for investigation or because the reactions from intravenous injections of some experimental serums were too severe to continue by that route. The usual precautions were carried out and included careful history concerning allergic tendencies and previous serum injections. Adrenalin was always made available for immediate use. Intracutaneous, conjunctival and, in some cases, treated with rabbit serum, intravenous tests⁹ were performed. Serum was

given to every case regardless of the history or the results of the various tests, these being used only as a guide for extra caution during the injections or for rearranging dosage.

In general, a total initial dose of 60,000 to 80,000 units was given to patients under 30 years, unless it was already known that the blood culture was positive. This dose was increased according to age and also approximately doubled: 1, when more than one lobe was involved; 2, when it was known that the blood culture was positive; 3, in pregnant or recently parturient women; or 4, in acutely ill patients when treatment was begun late in the disease. This predetermined original amount was given in divided doses at 2-hour intervals. The usual initial injections consisted of 1 to 5 cc., the second, 10 to 25, and the later ones, 20 to 45 cc., taking from 10 to 20 minutes for each injection. The serum was warmed to approximately body temperature before the injection and given undiluted, except in occasional instances where it was given in 2 to 10 parts of physiological salt solution.

Sulphanilamide was used only during the last year. Some patients received this drug before the pneumococcus type was determined and its administration was continued with or without serum thereafter. The combination of serum and sulphanilamide was used in some of the cases treated late in the disease, particularly if the blood culture was positive or if purulent complications were present or suspected. The usual routine was to give the drug orally, 2 gm. every 2 to 4 hours for 4 doses, and then 1 gm. every 4 hours. Dosages were changed, as necessary, depending on the course of the disease or the occurrence of untoward symptoms. When the blood values were determined,¹⁴ the doses were regulated in an effort to maintain a level of 10 mg. of the drug per 100 cc. of blood with a daily fluid intake of 3 to 4 liters. After the severe symptoms subsided smaller amounts were used, usually 4 gm. daily, in 4 to 6 doses. Bicarbonate of soda was given with each dose of the drug. The dosage was decreased or discontinued as soon as definite improvement was apparent, except in the presence of purulent complications. The usual precautions were taken and transfusions were used freely in patients receiving this drug over long periods. In the tables that follow, the cases receiving sulphanilamide are not segregated. The effect of this therapy will be considered separately below.

Results. Mortality. The crude death rates in the cases receiving specific antipneumococcic serums and in those treated without such serums are shown in Table 2. It is to be emphasized at the outset that we are not dealing with "controls." The non-serum treated cases are included here for comparison mainly because it is desirable to present, as nearly as possible, all the significant data concerning mortality. It will be noted that, although the proportion of cases of Type I pneumonia receiving serum has increased from 43 to 89%, the difference in mortality between the serum treated and non-serum treated cases has remained fairly constant.

Any presentation concerning the mortality from pneumonia is incomplete if it fails to consider the most important factors influencing the prognosis in this disease, namely: bacteremia, age and the presence of systemic complications. When serum is used, the stage of the disease when it is given and the amount are highly important. Each of these factors will be considered in turn.

TABLE 2.—MORTALITY IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Years.	Serum treated.			Non-serum treated.			Treated with serum, %
	No.	Died.	Died, %	No.	Died.	Died, %	
1929-35 ^{7c}	219	40	18	289	113	39	43
1935-36	68	12	18	61	27	44	53
1936-37	79	17	22	23	10	43	77
1937-38	93	16	17	12	5	42	89
Total	459	85	19	385	155	40	54

NOTE.—In this table and in those that follow, all cases receiving specific serum are included, regardless of time of treatment, complications or amount of serum. From the non-serum treated cases, those fatal cases in which the type was determined at autopsy were excluded. There were 13 such cases in the years 1929-35, 2 in 1935-36, 5 in 1936-37, and 3 in 1937-38. The 1937-38 serum treated cases include those treated with rabbit serums.

TABLE 3.—INCIDENCE OF BACTEREMIA AND ITS EFFECT ON THE DEATH RATE IN CASES OF TYPE I PNEUMOCOCCUS PNEUMONIA.

Years.	Cases treated with specific serum.							Cases treated without specific serum.						
	Blood cultures positive.			Positive blood cultures, %.	Blood cultures sterile.*			Blood cultures positive.			Positive blood cultures, %.	Blood cultures sterile.*		
	No.	Died.	Died, %.		No.	Died.	Died, %.	No.	Died.	Died, %.		No.	Died.	Died, %.
1929-35	69	25	36	32	150 ²⁷	15 ⁰	10	100	81	81	34	189 ⁶⁰	32 ³	17
1935-36	25	11	44	37	43	1	2	30	20	67	49	31 ⁷	7 ³	23
1936-37	33	12	37	42	46	5	11	7	5	71	30	16 ¹	5 ⁰	31
1937-38 Horse	33	10	30	43	44	4	9	3	3	100	25	9 ²	2 ¹	22
1937-38 Rabbit	7	1	14	44	9	1	11							
Total	167	59	35	36	292 ²⁷	26 ⁰	9	140	109	78	35	245 ⁷⁰	46 ¹²	19 ¹⁷

* Includes cases in which blood cultures were not done. The numbers of such cases are indicated in the superscripts.

Bacteremia (Table 3). It has previously been shown that treatment with specific serum either prevents the occurrence of bacteremia or clears the blood stream of bacteria in most cases where invasion has already taken place. It is not surprising, therefore, that the incidence of bacteremia among the serum treated cases increased during the past 3 years as relatively more of the severely ill patients were treated late in the disease. The death rates among both the bacteremic and non-bacteremic serum treated cases remained relatively low, as compared with the corresponding non-serum treated cases. The death rate among the bacteremic cases treated with rabbit serum appears to be comparatively low, but the number of cases is small and the age of the patients more favorable, as will be seen below.

There was an opportunity during these 3 years to observe the

results of more than one blood culture taken before beginning serum treatment in 27 bacteremic cases. In 19, all these cultures were positive and in 8 the earlier cultures were sterile and the one taken before the initial dose of serum was positive. The reverse was not observed in any serum treated case. After treatment, blood cultures became and remained sterile in 13 fatal bacteremic cases. In only 1 case were sterile blood cultures obtained before treatment and positive cultures later. This patient had empyema and extreme leukopenia. Among the non-serum treated cases the blood cultures were repeatedly positive in 11 cases, but 7 had sterile blood cultures first and then developed bacteremia while under observation.

TABLE 4.—INFLUENCE OF AGE, SPECIFIC SERUM THERAPY AND BACTEREMIA ON DEATH RATES. PNEUMOCOCCUS TYPE I PNEUMONIA. 1935-38.

Age group, yrs.	Cases treated with specific serum.*							Cases treated without serum.						
	Blood culture.				All cases.			Blood culture.				All cases.		
	Positive.		Negative.					Positive.		Negative.†				
	No.	Died.	No.	Died.	No.	Died.	Died, %.	No.	Died.	No.	Died.	No.	Died.	Died, %.
12-19 . .	8 ²	1	23 ⁴	0	31 ⁸	1	3	2	0	4	0	6	0	0
20-29 . .	14 ¹	2	37	0	51 ¹	2	4	1	0	14 ²	1	15	1	7
30-39 . .	27 ¹	9	38 ¹	3 ¹	65 ²	12 ¹	18	9	5	13 ¹	2 ¹	22	7	32
40-49 . .	22 ¹	5 ¹	32 ¹	4	54 ²	9 ¹	17	13	10	5 ¹	0	18	10	56
50-59 . .	14 ²	8	8	2	22 ²	10	45	7	6	12 ²	6 ¹	19	12	63
60-69 . .	9	5	4 ¹	2	13 ¹	7	54	6	5	4 ¹	2 ¹	10	7	70
70+ . .	4	4	4	4	100	2	2	4 ¹	3 ¹	6	5	83
Total . .	98 ⁷	34 ¹	142 ⁹	11 ¹	240 ¹⁶	45 ²	19 ¹³	40	28	56 ¹⁰	14 ⁴	96	42	44
	35% died		8% died					70% died		25% died				

* Includes cases treated with rabbit serums. The superscripts indicate the numbers so treated.

† Includes cases in which blood cultures were not done, the numbers of which are indicated by superscripts.

Influence of Age. In Table 4, the serum treated and non-serum treated cases occurring during the last 3 years are listed according to age and the results of blood cultures. The expected increase in death rate with advancing age is apparent in each instance. It would appear from these data that the greatest reduction in death rate from the use of serum occurred under the age of 50, although the basis for comparison is not entirely satisfactory in every age group. There may also have been some reduction in death rate among the treated cases in the sixth and seventh decade in spite of the relatively greater number of bacteremic cases treated. It is evident, from the manner in which cases were chosen for treatment, that relatively few severely ill patients in the younger age groups failed to receive serum. This may serve to explain the unusually low death rates among the non-serum treated cases in the second

and third decade, most of these cases having recovered at the time the type was determined.

Effect on the Death Rate of the Day of the Disease When Treatment is Begun. It was previously noted^{7c} that the death rate was considerably greater in cases of pneumococcus Type I pneumonia treated with specific serum after the fifth day of the disease than in those cases treated on the fifth day or earlier. When the experience of the last 3 years is added, the accumulated data indicate that there is a gradual increase in death rate after the fourth day, the greatest increase occurring after the sixth day (Table 5). Similar differences are noted in both bacteremic and non-bacteremic cases.

TABLE 5.—INFLUENCE OF THE DAY OF THE DISEASE WHEN SPECIFIC SERUM TREATMENT IS BEGUN ON THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Day treatment begun.	Years.	Blood culture positive.			Blood culture sterile or not done.			All cases.		
		No.	Died.	Died, %	No.	Died.	Died, %	No.	Died.	Died, %
Fourth day or earlier . . .	1929-35	37	11	30	95	6	6	132	17	13
	1935-38	61	16	26	118	6	5	179	22	12
	1929-38	98	27	28	213	12	6	311	39	13
Fifth day . . .	1929-35	12	3	25	25	2	8	37	5	13
	1935-38	14	6	43	12	3	25	26	9	35
	1929-38	26	9	35	37	5	13	63	14	22
Sixth day . . .	1929-35	6	3	50	15	3	20	21	6	29
	1935-38	11	4	36	8	1	13	18	5	28
	1929-38	17	7	41	23	4	17	39	11	28
Seventh day or later . . .	1929-35	14	8	57	15	4	27	29	12	42
	1935-38	12	8	67	4	1	25	16	9	56
	1929-38	26	16	62	19	5	26	45	21	47

Dosage. The general scheme according to which the doses were arranged has been mentioned. During 1936-37 relatively small doses were used, as recommended in the Massachusetts Pneumonia Program, namely, 60,000 units for the initial dose in all patients, regardless of age.¹² During the following year the initial dose was gradually increased except in the younger patients. Larger initial doses were given throughout this period under the conditions mentioned above and treatment was continued if the therapeutic response was not adequate. The average doses used during each of the 3 years are summarized in Table 6. Smaller amounts of rabbit serums were used chiefly because during this period these serums were treated as experimental and were given chiefly to younger patients or to those in the best general condition and with relatively milder disease. The average dose of antibody was increased considerably during these 3 years, particularly in the older patients and in those with positive blood cultures.

TABLE 6.—ANALYSIS OF AVERAGE DOSES PER PATIENT OF PNEUMOCOCCUS TYPE I ANTIBODY. 1935-38.*

	1935-36.	1936-37.	1937-38.		
			All cases.	Horse serum.	Rabbit serum.
Volume, cc.	44	52	81	93	23
Units† (thousands)	101	138	200	214	129
Units per cc.	2270	2650	2470	2300	5610
Number of injections	3.5	3.9	5.3	5.8	2.6
First injection (thousands of units)	5	9	7	7	21
Subsequent injections	38	44	45	43	68
Total dose per patient:					
Recovered cases	97	132	185	214	124
Fatal cases	119	162	269	284	165
Non-bacteremic cases	87	114	144	152	105
Bacteremic cases	125	170	273	300	160
Age group: 12-19 years	96	100	126	158	94
20-29 years	99	120	171	172	150
30-39 years	109	149	186	180	203
40-49 years	108	128	227	239	100
50-59 years	88	149	240	254	178
60-69 years	55	152	278	293	200
70 years and older	173	415	415	
Average age (years)	34.4	37.5	36.8	38.2	30.2

* For the years 1929-35 (76) the average amount of serum used per patient was 94 cc., containing 147,000 units or 1560 units per cc.

† The number of units given on the labels was 10 to 40% lower than these actual values obtained on standardization.

Untoward Reactions. The numbers of cases exhibiting various reactions are listed in Table 7. It will suffice to mention some of the interesting features of the reactions in each of the main groups.

TABLE 7.—OCCURRENCE OF UNTOWARD REACTIONS IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA TREATED WITH CONCENTRATED SPECIFIC ANTIBODY. 1935-38.

	Horse serums (224 cases).	Rabbit serums (16 cases).
Immediate reactions	21 (9%)	0
Nausea and vomiting after one or more doses	7	
Urticaria	6	
Palpebral edema and asthma	1	
Dyspnea and wheezing (asthma)	6	
Fainting	1	
Delayed serum sickness	52 (23%)	5 (31%)
Fever alone	5	1
Arthralgia	28	1
Urticaria	7	0
Arthralgia and urticaria	12*	3
Thermal reactions	66 (31%)	7 (44%)
Single chill	45	5
Chill after each of 2 injections	17	2
Chill after each of 3 injections	4	
Only after initial injection	10	3
After initial and later injection	16	2
Only after second and/or later injections	40	2
Lederle serums supplied for clinical trial (74 cases)	6 (8%)	
State supply† (150 cases)	60 (40%)	
1935-36 (63 cases)	25 (40%)	
1936-37 (32 cases)	3 (9%)	
1937-38 (55 cases)	32 (58%)	

* Two of these patients had asthma during this attack, 1 had enlarged nodes, 1 had purpura and thrombopenia, and 1 had 2 bouts one week apart.

† Including some used for clinical trial.

Immediate Reactions. Nausea and vomiting and vague pains and discomforts usually followed the injection of lots of serum which gave thermal reactions, frequently, in the same or in other patients. Among the 6 patients who had urticaria soon after receiving serum, this reaction occurred after the first dose in 1 case, after the second dose in 1, after the third in 2 cases, after the third and fourth doses in 1, and only after the fourth injection in 1 case. Only 2 of these 6 patients gave positive skin tests for horse serum and one other had a history of previous serum injection (tetanus antitoxin). Palpebral edema, asthma and fainting occurred only in patients with a personal or familial history of asthma. Only 2 patients among those exhibiting immediate reactions later had serum sickness. The large majority of the patients with a history of allergic manifestations or of previous serum injections, as well as those giving positive skin tests, had no immediate reactions following the therapeutic injections.

Thermal Reactions. These usually consisted of mild chills occurring almost uniformly about 1 hour after the injections and were followed by rises in fever of 1 to 4° F. They were less common after the small initial doses of 2 to 5 cc. In some patients the first chill occurred after the fourth or even a later injection which was no larger, and sometimes even smaller, than the preceding injections of serum of the same lot. Chills have occurred in many instances in spite of the use of generous doses of aspirin prior to the injection (used during 1937-38). It is possible, however, that some chills may have been averted or were less severe when this drug was used. While the large majority of patients suffered no serious consequences from these chills and, in fact, often had an exaggerated sense of well-being following them, they were sometimes distinctly harmful. In elderly or debilitated individuals and in other severely ill patients treated late in the disease, even mild chills were followed by a seemingly premature development of circulatory collapse and/or pulmonary edema and a fatal issue may have been hastened in this manner. Similar episodes occasionally followed the more severe reactions in younger individuals who were in good general condition. Such severe reactions were observed in 1 patient treated with horse serum and in 2 patients treated with experimental lots of rabbit serum. All 3 were resuscitated after vigorous treatment for the hyperpyrexia and the generous use of stimulants. Chills were unusually frequent with the serums recently supplied by the State Laboratory, but this varied in different years.

Serum Sickness. The incidence of serum sickness among the cases treated with horse serums was 23% and was almost exactly the same in each of the last 3 years. It was also the same among the cases treated with the Lederle serums as among those treated with the serums provided by the state, although these serums differed in their chill-producing properties. The symptoms of

serum sickness were almost always mild. In only 2 cases was the arthralgia severe and difficult to control with ordinary analgesic drugs. The urticaria was easily relieved by small doses of adrenalin. The symptoms usually lasted from a few hours to 3 days.

Clinical Response. The character of the symptomatic response to serum therapy during the past 3 years was similar to that previously noted.^{7c} Among the 195 recovered cases, 159 (82%) were afebrile and free of symptoms of the acute disease within 48 hours after the first injection of serum, and 109 (56%) had passed the crisis within 24 hours.

Empyema developed in 21 (11%) of the serum treated patients who recovered. Of these, 17 had positive blood cultures before treatment representing 26% of the serum treated bacteremic survivors, and 4 had sterile blood cultures, or 3% of the non-bacteremic cases who recovered after serum treatment. The latter 4 patients were all treated on the fourth day. In 1 of these cases the fluid was sterile after the first tap and resorbed spontaneously. A second had a putrid empyema complicating a lung abscess and no pneumococci could be cultured from the pleural fluid. Among the bacteremic patients who developed empyema, serum treatment was begun on the second day in 1 patient (this patient received only 100,000 units of which the first 60,000 were given intramuscularly), on the third day in 2, on the fourth in 6, on the fifth in 3, on the sixth in 4 and on the seventh in 1 patient. Rabbit serum was used in the treatment of 3 of these cases, including one who received only 90,000 units intramuscularly on the fourth day and 2 who received 250,000 and 300,000 units, respectively, on the third and sixth days. Surgical drainage was employed in the treatment except in the patient mentioned above whose fluid became sterile and resorbed spontaneously and one of the rabbit serum recipients who was treated by repeated thoracentesis over a period of 6 weeks.

Other Complications in Recovered Cases. Sterile effusions were demonstrated in 10 serum treated cases. All the 10 patients were treated before the fourth day and the fluid resorbed spontaneously in each instance. Only 1 of these patients had a positive blood culture; this patient received 180,000 units on the second day of the disease. *Septic parotitis* developed during convalescence in 3 of the non-bacteremic serum treated cases, but no pneumococci could be cultured from the parotid pus in any instance. Two bacteremic patients treated after the seventh day developed abscesses of the leg from which Type I pneumococci were cultured. One of the patients with empyema also had purulent subdeltoid bursitis (and arthritis) with Type I pneumococci in the exudate.

Among the 54 non-serum treated patients who recovered, empyema developed in 6 (11%), including 3 of the 12 bacteremic and 3 of the 42 non-bacteremic cases. Sterile effusion was demonstrated

in 1 case and otitis media and mastoiditis occurred in another. The blood cultures were sterile in the 2 latter cases.

Fatal Cases. Since none of the specifically treated cases have been excluded in determining the death rates given in the various tables, it will be of interest to note briefly some of the factors contributing to the fatal outcome in the individual cases. Multiple factors were operative in many of the cases but only the most important ones will be mentioned.

There were 15 cases in which the pneumonia occurred as a complication of other serious disease. These included: diabetic coma 2, uremia 1, decompensated valvular rheumatic heart disease 3, arteriosclerotic heart disease with auricular fibrillation and failure 3, cerebral thrombosis with hemiplegia 1, induced abortion with overdose of ergotamine 1, massive hemorrhage with severe anemia 2, prostatic obstruction with peripheral neuritis and later parotitis 1, and lung abscess following tonsillectomy 1. In 4 patients death was probably due to superinfection. These included: 1 with mediastinitis and 1 with pericarditis, each due to hemolytic streptococci, and 2 patients in whom Type I pneumococci were found only in the first sputum and later ones showed only hemolytic streptococcus in the one and *Staphylococcus aureus* in the other. Purulent pericarditis was present in 3 cases (1 also had vegetative endocarditis) at the time treatment with serum was begun. Although many alcoholic patients are included among both the recovered and the fatal cases, there were 5 in whom the alcoholism was probably a major factor in the fatal outcome. Two of these patients were admitted in deep alcoholic coma from which they were never completely roused and 3 had very active delirium tremens which resisted all measures, and death occurred suddenly during violent muscular hyperactivity after apparently good response to serum. There were 9 patients whose general condition at the time the type was determined was so poor that vigorous measures had to be taken to combat peripheral vascular collapse and pulmonary edema before treatment with serum could be undertaken or carried through. In some of these cases it was considered unwise to continue with serum treatment after the first or second injection even when untoward reactions were not manifest. In 3 other patients treatment was inadequate for other reasons. One of these was thought to be Type II on the basis of the Neufeld typing, was treated vigorously with serum for this type until bacteremia developed and Type I was obtained from the blood culture. At this time the patient was *in extremis* and only one dose of Type I serum could be given before he expired. The second patient was given a total of 100,000 units although bacteremia and massive empyema were present at the time. The third was a bacteremic patient who received 75,000 units each on the fourth and fifth day during which the pulmonary lesion extended and then meningitis developed in

spite of further doses of 100,000 units during each of the next 2 days. Finally, there were 3 patients with sterile blood cultures before serum treatment, who were apparently improved following a moderate dose but suddenly became worse. One of these had a large empyema and leukopenia and later developed bacteremia.

Cases Treated With Rabbit Serums. (See Tables 3, 4, 6 and 7.) It has already been noted that, owing to the experimental nature of these serums, they were first used in the treatment of younger adults and in others who appeared to be in good general condition. Various experimental methods were used in the concentration of these serums. Of the 16 patients with pneumococcus Type I pneumonia treated with these rabbit serum concentrates, 2 died. Blood cultures were positive before treatment in 7 patients, of whom 1 died. This was a 56-year-old patient treated on the fifth day of the disease. He was in mild circulatory collapse at the time and became comatose after only 2 doses containing 55,000 units had been given and died 17 hours later. Autopsy revealed bilateral atypical pneumonia with empyema and purulent pericarditis. Empyema developed in 3 of the bacteremic survivors. One of the patients, a 14-year-old boy, received only a single intramuscular injection of 90,000 units on the fourth day and felt sufficiently improved in 12 hours so that no further specific therapy seemed indicated. The non-bacteremic patient who died had 4 other "higher" types of pneumococci in his sputum in addition to the Type I, but culture of the sputum before death showed an almost pure growth of *Staphylococcus aureus*. This patient and 1 of those with empyema also received sulphanilamide and are listed below (Cases 7 and 11, respectively, in Table 8).

The clinical response in the patients who recovered was similar to that observed in cases treated with horse serum. In 6 cases, including 1 with empyema, crisis occurred in less than 24 hours, in 4 it occurred between 36 and 48 hours, and in 2 it was delayed more than 48 hours after the first dose of serum.

The average amount of antibody per patient was considerably less than in the cases treated with horse serum and, owing to the higher average concentration of the antibodies, the volume injected was much smaller (Table 6). This was probably related, in large part, to the choice of cases. There were no immediate reactions of the "allergic type" (urticaria, asthma, etc.) observed following the injections of rabbit serums, but thermal reactions and serum sickness were somewhat more frequent than among the horse serum recipients (Table 7).

Cases Treated With Sulphanilamide. In general, the cases of Type I pneumococcus pneumonia selected for treatment with sulphanilamide alone, or combined with specific serum were severe cases, seen late in the disease, particularly those with positive blood cultures, or cases with focal or systemic complications or with

mixed infections. In some cases the drug was given only after the latter conditions became evident. The more pertinent data in these cases are listed in Table 8.

TABLE 8.—RÉSUMÉ OF CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA RECEIVING SULPHANILAMIDE WITH OR WITHOUT SPECIFIC SERUM. 1937-38.

Case.	Sex and Age.	Blood cultures.	Lobes involved.	Specific serum.		Sulphanilamide.			Termination: mode, day.	Remarks, complications.†
				Day begun.	Units × 1000.	Days given.	Total, gm.	Mg./100 cc. in blood.‡		
SERUM-TREATED CASES.										
1	M 30	Pos. 4, 6, 8; Neg. later	Rl	7	650	8-21	84	2.5; 1.7	LS-12	2 transfusions; leg abscess drained 22d day.
2	F 38	Pos. 6; Neg. later	Lu	7	140	7-14	36	9.1	C8	Sulphanilamide continued after crisis.
3	F 19	Neg. 4, 5	Ru	4	340	4-5	6	..	C5	Normal premature delivery 1 month later.
4	M 69	Pos. 8; Neg. 9, 10, 11	RlLl*	8	300	9-14	32	9.0	D14	Cerebral thrombosis preceded pneumonia.
5	M 43	Pos. 10 (?); Neg. later	Lu	10	280	10-36	90	..	L24	Phlebitis; leg abscess drained 12th day.
6	M 44	Pos. 5, 6; Neg. 2, 3, 8, 12	Ru	6	400	6-24	80	3.6; 4.6	LS-9	Some pulmonary edema before treatment.
7	M 33	Neg. 3-8	Ruml	3	R270	6-10	16	..	D10	Staph. aureus predominating in sputum.
8	M 74	Pos. 4; Neg. later	Rl	4	280	16-19	15	..	D19	Improved after serum; drug given for parotitis.
9	F 32	Neg. 7	Ruml	7	200	7-8	8	..	D8	Mild collapse and auricular fibrillation before treatment.
10	F 23	Pos. 4, 5; Neg. later	RulLl	4	550	8-12	20	7.6	L12	Otitis media (strep.).
11	M 57	Pos. 6, 7; Neg. later	Ruml	6	R300	6-13	44	3.8; 5.6	Emp.	Transfusions 13th and 20th days.
12	F 46	Neg. 5, 8, 14	Ruml	5	150	5-14	74	10.4	L13	Transfusion 14th day.
13	M 43	Pos. 5, 11, 13; Neg. 6-10	RlLl	5	540	8-19	73	..	D19	Delirium tremens; endocarditis (?).
NON-SERUM TREATED CASES.										
14	M 19	Neg. 4, 5, 7	Ll	6-11	32	..	C7	Drug continued after crisis.
15	M 71	Pos. 7, 8, 9	RulLl*	7-9	18	..	D9	Cardiacdecompensation; auricular fibrillation.
16	M 66	Neg. 18 and autopsy	Ruml	18-24	64	..	D25	Strep. and Pn. XIII (sputum); empyema and pericarditis (Pn. I).
17	M 62	Neg. 3, 5, 6, 7	Ruml	6-9	22	..	D9	Extended Rml, 6th day.
18	M 40	Neg. all	RlLu	30-38	32	..	D48	Emp. neg. first, then strep. and fusiform bacilli; rib resection.

* Atypical consolidation.

† Anemia with a drop of more than 20% hemoglobin occurred in Cases 1, 4, 11 and 13 and a papular rash developed in Case 12.

‡ Unheated (14).

ABBREVIATIONS: Sex: M = male, F = female. Lobes: R = right, L = left, u = upper, m = middle, l = lower. Blood cultures: Pos. = positive for Type I pneumococcus. Neg. = negative; the numerals represent days of disease. Termination: C = crisis, L = lysis, D = died. Specific serum: Units = compared with the National Institute of Health Standard serum, P11, to which a value of 300 Type I units is assigned. R = rabbit serum.

Among the 5 cases treated with the drug but without serum, bacteremia was present in 1, and was not affected by the drug. In the other 4 cases, all blood cultures were sterile in spite of a fatal outcome in 3 of them. In fact, the only patient who recovered was a young, non-bacteremic patient treated late in the disease in whom crises occurred within a few hours.

The combined treatment was used in 13 patients. The average age of these patients was 42.4 years; the average amount of antibody used was 338,000 units per patient, and of sulphanilamide 44 gm., the latter given over an average of 7 days. Blood cultures were positive before treatment in 9 of these cases. In Case 1, the blood culture was still positive after the first course of treatment with serum alone but became and remained sterile after sulphanilamide and more serum were given. In Case 11, the blood culture remained positive after 1 day of the combined therapy. In 4 of the remaining bacteremic cases all the blood cultures were sterile after treatment with serum given alone or with the drug. In Case 13, however, 5 daily blood cultures were sterile after treatment was begun, but 2 cultures taken later again showed Type I pneumococci. This patient developed a cardiac murmur and probably had vegetative endocarditis, but embolic phenomena were not recognized and autopsy could not be obtained to confirm this diagnosis. In only 2 of these 13 cases was a good clinical response rapidly obtained (Cases 2 and 3).

Discussion. Data presented confirm numerous previous observations by many physicians that specific antibody is a highly effective curative agent in the treatment of pneumococcus Type I pneumonia, especially when used early and in adequate amounts.^{1,3-5,7,12,17,18,20} In the present cases, as in other similar groups, the deaths have been limited, for the most part, to well-defined groups of cases, namely, those with severe systemic disease, or with other complicating infections, those given inadequate amounts of antibody or in whom the treatment was begun late in the disease in the face of impending circulatory collapse or pulmonary edema or in the presence of serious focal complications.

While many new forms of physical, chemical and biologic agents are advocated from time to time as panaceas in the treatment of pneumonia, none thus far proposed is so thoroughly supported by both experimental and clinical evidence as is the use of specific antibody in cases due to Type I pneumococcus. Two recent important advances in therapy, however, warrant special consideration, namely, specific antibody produced in rabbits^{9,10} and the recent chemotherapeutic agents as exemplified by sulphanilamide. It would be out of place to consider here the theoretical considerations which prompted the clinical trial of antipneumococcus rabbit serums¹⁰ or the experimental basis for anticipating beneficial results from the use of sulphanilamide.^{2,8,16} We are concerned, at the moment, with an evaluation of the practical clinical results.

Since the comparative studies of horse and rabbit serums were made primarily with Type I antipneumococcus serums and since more clinical data are available for this than for any other type, it is reasonable to attempt first a comparison of results in cases due to this type. A critical consideration of the data presented makes

it obvious that such a comparison will be difficult until a considerably larger number of cases are treated with rabbit serum under conditions similar to those prevailing in the cases treated with antibody produced in horses. For that purpose all the significant data concerning both the antibody and the patients should be available for comparison.

The number of cases treated with rabbit serums in this present series is small, but they bring out several important features. *Concentrated* antibody was used and administered with ease and safety. No doubt additional experience will reduce the hazards still further. Indeed, the more recent lots of concentrated rabbit serums have given no more frequent thermal reactions than most similar horse serums. The immediate type of "allergic" reactions (urticaria, asthma, etc.) have been less frequent with rabbit serums, as might be expected. Thermal reactions and delayed serum sickness, however, are no less frequent either in this series or with the unconcentrated serums used elsewhere.^{9,13} It is already evident from the combined experiences now available^{9,13} that empyema does occur even when adequate amounts of rabbit serum antibody are used and that the incidence of this complication is probably no less frequent than in cases treated with horse serums.

As to the comparative amounts of antibody, in terms of volume or of units, that are necessary to produce optimum clinical results, it is still more difficult to draw conclusions. Although the cases were not entirely comparable, the dosage of rabbit serum used in our small series was appreciably smaller than the average dose of horse serum. The latter, in turn, is considerably smaller, both in volume and number of units, than the average amount of unconcentrated rabbit serum used at the Rockefeller Hospital⁹ or by Loughlin *et al.*¹³ The experience with horse serums has been sufficiently convincing with regard to the superiority of concentrated over unconcentrated serums that the use of the latter has been practically abandoned. It seems to us that the aim should be to produce the most potent concentrates that can be given with the least untoward effects unless it can be shown, with reasonable certainty, that there are effective agents in the unconcentrated serums which cannot be retained by proper concentration.

The death rates in the cases treated with rabbit serum both here and elsewhere indicate the striking benefits of this agent. However, they cannot be interpreted as indicating any superiority over concentrated antibody produced in horses. Thus, although there was only 1 death among 25 rabbit serum treated cases reported from the Rockefeller Hospital, no deaths were noted from the same number of cases treated with concentrated horse serums in the same hospital during the preceding 2-year period. In the 28 cases reported by Loughlin *et al.*¹³ the death rate was 10.7%. These authors, however, excluded from their series those patients "for

whom serum was used as an auxiliary therapeutic measure and who at autopsy showed disease processes of themselves lethal." The number and character of these cases are not detailed. In the present series of cases it is possible to reduce the death rate in the cases treated with horse serum to as low as 3%, depending on which of the fatal cases one chooses to exclude on similar grounds.

At the moment, it is fair to conclude only that type-specific pneumococcus antibody produced in both horses and rabbits are highly effective curative agents. Perhaps the greatest advantage of Type I antipneumococcus rabbit serum is that it can be given without immediate "allergic" reactions to certain sensitive patients, particularly those who have previously received injections of horse serum.

It is natural that, where an effective specific agent is available, the use of non-specific agents like sulphanilamide should be reserved only for special groups of cases. The bacteriostatic action of this drug may be used for the purpose of enhancing the action of specific antibody^{2,8,16} and may prove useful where bacteremia is present late in the disease at a time when antibody itself is likely to be less effective. It may be particularly useful in the treatment of superinfections with hemolytic streptococci which often vitiate the good specific effects of antipneumococcic serums.

The cases in which we used the drug were of the sort that are most likely to be chosen for this therapy. No definite conclusions can be drawn from so small a group; but it would seem that, considering the very poor prognosis in those patients given the combined treatment, the drug was beneficial when used in this manner. By itself, however, it was not very effective. To be sure, in 3 of the fatal cases, it may have prevented the occurrence of bacteremia or at least made it difficult to demonstrate the bacteria in the blood stream by the usual methods. However, it did not readily clear the blood stream of Type I pneumococci in the case in which it was used after invasion had already occurred. In 1 of the cases, bacteremia recurred in spite of the combined treatment. Focal infections harboring large numbers of Type I pneumococci were demonstrated during life or at autopsy after several days of treatment with this drug alone or with specific antibody. These facts would indicate that the drug, at least in the manner in which it was used, was not regularly effective in helping to rid the body of this organism. It is possible that larger doses, more carefully controlled to maintain higher concentrations in the blood, would be made effective. It has been difficult to maintain high levels in pneumonia patients with oral doses that are usually considered adequate.

The introduction of large numbers of new chemotherapeutic agents makes it increasingly difficult to obtain proper clinical evaluation. A word of caution concerning their use in cases of pneumonia or other pneumococcic infections may be in order. In

undertaking clinical trials, the non-specific character of the action of these drugs may be taken by clinicians as an excuse for omitting adequate bacteriologic controls. Such omissions would make it impossible properly to estimate their value in these conditions.

Summary and Conclusions. The death rate among cases of Type I pneumococcus pneumonia treated with concentrated type-specific antibody at the Boston City Hospital has been regularly one-half or less that of similar contemporaneous non-serum treated cases. This has remained true in recent years in spite of the fact that the proportion of cases treated with serum has increased from 43 to 89%. In the cases treated with serum before the end of the fourth day the death rate is less than one-third of the non-serum treated mortality.

Bacteremic and non-bacteremic cases are equally influenced. The greatest reduction in death rate occurs in patients under 50, but those of other age groups are probably also beneficially affected by serum treatment. Empyema occurred after serum treatment chiefly in bacteremic patients, and its frequency was proportional to the delay in beginning treatment.

Type I antipneumococcus serums produced in both horses and rabbits were potent and effective. There are insufficient data to indicate any superiority of the one over the other. There were no immediate allergic type of reactions observed in the rabbit serum recipients, but thermal reactions and serum sickness were somewhat more frequent among them.

Sulphanilamide in the small number of cases in which it was used alone or with serum seemed to influence the course of Type I pneumococcus pneumonia only slightly, if at all.

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SULPHANILAMIDE IN THE TREATMENT OF GONOCOCCAL ARTHRITIS.

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THERE are now a large number of reports dealing with the effect of sulphanilamide in the treatment of local gonococcal infections, including urethritis, pelvic inflammatory disease, and ophthalmia. In a discussion of the pathogenesis of gonococcal arthritis and the mode of recovery, together with its treatment, Keefer and Spink^{7a} called attention to the fact that sulphanilamide was capable of sterilizing the synovial fluid within a short time after its exhibition by mouth.

More recently, we have found that when sulphanilamide is added to whole blood, or is given by mouth so that it is present in the plasma, the bactericidal power of the blood increases. We have also shown that the bactericidal power of the synovial fluid increases following its use and gonococci may be killed off rapidly in its presence. For these reasons we have studied the effects of sulphanilamide in a group of 14 cases of gonococcal arthritis.

Before presenting our results it is well to review a few of the salient facts concerning gonococcal infection of the joints. From our studies^{2a, 7a, b, d} it is convenient to divide the cases into three groups on bacteriologic and immunologic grounds: 1, Cases with a local lesion, bacteremia, and metastases in the joints from which organisms can be obtained; 2, cases with a local lesion, sterile blood, and infected joints; 3, cases with a local lesion, sterile blood, and sterile synovial fluid.

When the first group of cases is studied immunologically it is found that the blood and synovial fluid contain no demonstrable

antibodies, but when the blood is cleared of organisms antibodies can be demonstrated therein.

Recovery occurs when the blood and synovial fluid are sterilized and the damage caused by the organisms and their products has been repaired. Such an illustrative case was reported in a previous paper.^{2b}

In the second group of cases, namely, those with a local lesion having no evidence of bacteremia, but with infected synovial fluid, there are antibodies in the blood against the homologous strain of organisms but none in the synovial fluid.^{2a} The synovial fluid is sterilized when the antibodies increase so that they are present in excess.

In the third group, there are two subdivisions: *a*, Cases with a local lesion, no bacteremia, and sterile synovial fluid, with antibodies of relatively high titer in the blood and synovial fluid; *b*, cases with a local lesion, no bacteremia, sterile synovial fluid, and no demonstrable antibodies in either the blood or synovial fluid. The former is the common finding, the latter is an uncommon occurrence but of great interest and significance. From these cases it might be argued that some of them are not due to gonococcus infection. However, the clinical course and the subsequent appearance of antibodies in these patients are strong points in favor of the diagnosis of gonococcal arthritis. The observations of Ralston⁶ on the effects of gonococcal toxins or sterile autolysates (Corbus-Ferry filtrate) are of great significance in understanding the possible origin of this type of arthritis. It is known that these products are exceedingly histiotoxic for skin, the urethra, and the joints; and when this material, which is antigenic, is injected into horses, the commonest finding is the development of an acute polyarthritis. Here, then, is an experiment in which acute polyarthritis is produced by injecting *sterile toxic* products from the gonococcus and, while it has not been proved as occurring in man, there is suggestive evidence at least that this mechanism may be important in some cases of arthritis in man, and in particular the cases with a local lesion and arthritis without demonstrable antibody formation until late in the disease.

In assessing any form of treatment of gonococcal arthritis, then, it is necessary to take these various factors and types of reaction into account. In a review of the treatment of 70 cases of gonococcal arthritis, Spink and Keefer^{7c} recorded that the patients who have the worst outlook insofar as complete recovery from the arthritis is concerned are those falling into the second group. Those with the best outlook are the ones with pain and periarticular swelling, with very little effusion into the joints.

For the above reasons, we have divided our cases into three groups: 1, those with infected synovial fluid; 2, those with sterile synovial fluid; 3, those without effusion of fluid into the joints.

TABLE 1.—SUMMARY OF CASES.

Age. Sex.	Duration of arthritis before drug (days).	Joints involved.	Duration of arthritis after drug (days).	Total amount of drug (gm.).	Duration of fever (days).	Reactions.	Hospital stay (days).	Local focus.	Results.
<i>Patients With Infected Synovial Fluid.</i>									
49 ♂	10	Right and left knee	12	4	14	None	31	*	R
22 ♂	5	Right and left knee, right shoulder,	63	6	30	None	84	S	R
34 ♀	8	right ankle.	21	3	21	Nausea, vomiting, anemia	42	S	R
40 ♂	10	Metacarpal phalangeal, knees,	10	3	82	3	16	*	R
41 ♀	7	hips, right wrist, left knee	28	7	12	9	84	S	R
		Both knees				Anemia			
<i>Patients With Sterile Synovial Fluid.</i>									
24 ♂	6	Right knee	10	...	48	Afebrile None	14	S	R
40 ♂	7	Left knee	11	...	54	4	..	*	R
						Recurrence of arthritis and fever following withdrawal of drug			
52 ♀	7	Right knee	10	...	21	13	25	*	R
30 ♂	10	Right knee	14	...	22	16	..	S	R
						Hemolytic anemia			
<i>Patients Without Joint Effusions.</i>									
30 ♂	7	Right ankle, metacarpal phalan-geal	4	...	78	14	42	S	R
						Recurrence of arthritis on withdrawal			
36 ♀	3	Left knee, wrists, ankles, hands	4	...	76	16	42	S	R
42 ♂	2	Left ankle	3	...	64	5	28	S	R
22 ♀	4	Left elbow, right wrist, fingers right hand	1	...	20	2	5	†	I
32 ♂	3	Knee, costo-sternal	6	...	78	4	35	N.S.	I
						None			

* Local focus undetermined.
 R Recovered completely.

S Sterilized by sulphanilamide alone.
 I Improved.

N.S. Not sterilized.
 † Study incomplete.

Patients With Infected Synovial Fluid. From our previous experience⁵ approximately 30% of patients with gonococcal arthritis have an infected synovial fluid at the time of our examination. Moreover, it is in this group of patients that the prognosis is less certain insofar as complete recovery of normal function of the joints is concerned, and they remain in the hospital the longer period of time. The average hospital stay in previously studied patients was 61 days.

In the present group, there were 5 patients with infected synovial fluid who were treated with sulphanilamide. The end results were surprisingly good in spite of the fact that the disease frequently remained active for a long period of time. They all recovered completely and without any permanent disability of the joints. The course of the disease varied from 16 days to 3 months and the main features have been summarized in Table 1.

There are certain features requiring comment. First of all, it was clear that sulphanilamide diffused into the synovial fluid in about the same concentration as that of the blood. Secondly, the synovial fluid was sterilized in from 3 to 7 days and in only 1 case were organisms found in the synovial fluid after sulphanilamide had been started. In this case, it is possible that the dosage was inadequate, since it was one of the first cases treated and quantitative studies of sulphanilamide in the synovial fluid were not made. When we have maintained the sulphanilamide control of synovial fluid above 5 mg. %, the fluid has been sterilized with regularity.

Sulphanilamide did not interfere with the appearance of antibodies, such as the complement-fixation reaction, so that it would appear that immune reactions were neither delayed nor prevented. This is significant since there is some evidence that the final destruction of the organism is due to the combined action of the chemical and the normal defense mechanism of the body. For example, too early withdrawal of the drug may be followed by a recurrence of the arthritis, fever, and an exacerbation of the urethritis. The temperature curve may not be strikingly altered for some days following its use.

It would appear from the study of these cases that, in spite of the sterilization of the synovial fluid within a relatively short period of time, the damage to the synovial membrane may require a long period for recovery. The end results, however, are most encouraging and certainly in our experience so far, at least, they are better than the other methods that we have employed in the past.

Figure 1 is a chart showing the course of events in a patient with an infected synovial fluid. In short, this 40-year-old man had been well until 2 weeks prior to admission to the hospital when he developed an acute respiratory infection which subsided within 4 days. Five days before admission to the hospital his right knee became stiff and painful and the next day it was greatly swollen. The only

point of significance in his past history was the occurrence of gonorrhea 20 years previously.

The examination showed nothing significant except the acute arthritis of the right knee, high fever, and leukocytosis of 12,300 per c.mm. No gonococci were recovered from the urethra or prostatic fluid. The figure shows that the synovial fluid was infected with gonococci when it was examined after the first tapping, and the gonococcal complement-fixation test on the blood was positive. Following sulphanilamide by mouth, the sulphanilamide content of the blood and synovial fluid increased so that at the time of the second tapping the synovial fluid was sterile and contained 5.7 mg. of sulphanilamide per 100 cc. Two days later the synovial fluid

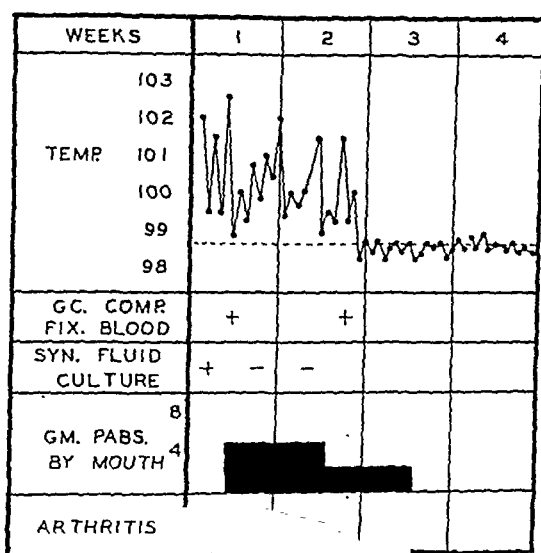


FIG. 1.—Patient with gonococcal arthritis with infected synovial fluid. Sterilization of synovial fluid following sulphanilamide when the concentration reached 5.7 mg. per 100 cc.

contained 7.7 mg. of sulphanilamide per 100 cc. The fever gradually subsided and the arthritis disappeared so that he was well, without any disability, at the end of 4 weeks.

This case shows that the synovial fluid can be sterilized before the temperature returns to normal but, following the sterilization, the arthritis begins to improve. Moreover, it illustrates the fact which has been stressed by us before^{7c} that gonococcal infection of the joints may appear following a latent period after a primary infection, and it may be impossible to isolate the organisms from the genito-urinary tract and, secondly, these instances of arthritis not infrequently follow an attack of acute sore throat. Finally, there seems to be no question that the course of the arthritis was favorably influenced by sulphanilamide.

Patients With Sterile Effusions Into the Joints. All of the 4 patients of this group recovered without disability or deformities of the joints. The local lesion in the genito-urinary tract was sterilized in 3 of the cases on sulphani-*l*amide alone. The duration of the fever was shortened, the effusion in the joints subsided rapidly, and the patients were improved in a shorter period of time than in similar cases treated with sulphani-*l*amide. In a group of 22 similar patients treated without sulphani-*l*amide, the average duration of their stay in the hospital was 53 days. In the 4 cases of the present group, it was 14, 21, 23 and 40 days, respectively, the average being 24 days.

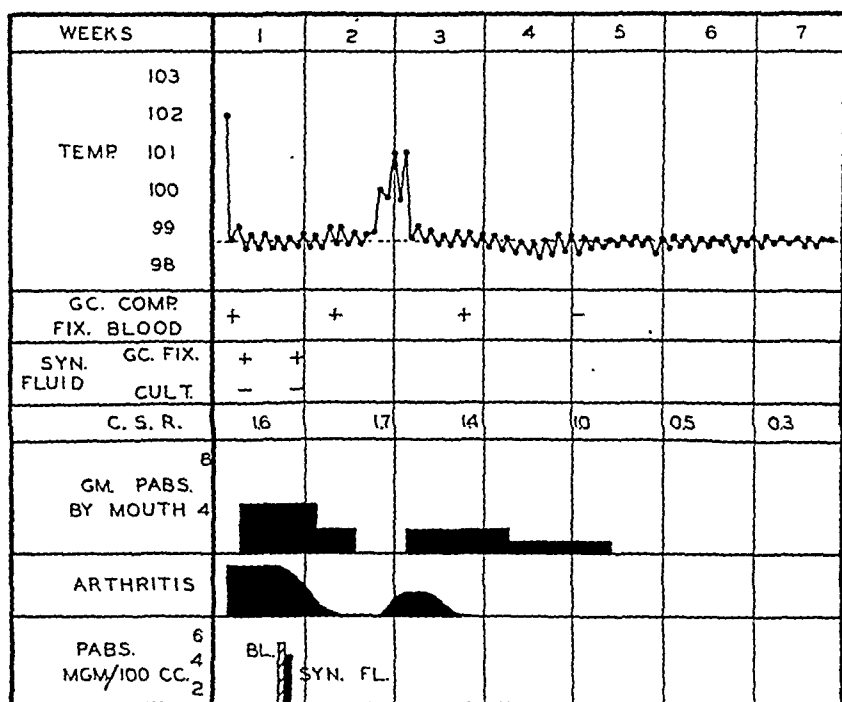


FIG. 2.—Patient with gonococcal arthritis, sterile synovial fluid, increased sedimentation rate, exacerbation of arthritis with withdrawal of fluid, positive gonococcal complement-fixation test.

One of the patients developed a hemolytic anemia from which she recovered following blood transfusion and a cessation of the drug. In another patient, there was a recurrence of fever and an exacerbation of the arthritis following its withdrawal (Fig. 2). In this patient, the symptoms subsided following the use of the drug once again. The story of this patient's illness was as follows:

Clinical History.—A man, aged 40, developed an acute arthritis of the left knee joint 7 days before admission to the hospital. The examination showed swelling, tenderness, and an effusion of fluid into the left knee joint, fever, and leukocytosis of 13,600 per c.mm. The gono-

A woman, aged 36, complained of pain and tenderness in the right shoulder and elbow and in the left knee. The examination showed the left knee to be swollen, red, and tender together with pain and tenderness in the right shoulder and elbow. She had fever and 10,700 leukocytes per c.mm., and the cervical smear was positive for gonococci and these organisms were grown from the exudate. The course of the illness is shown in the figure. During the first 10 days of observation her temperature fluctuated between normal and 102° F., and the arthritis persisted. The gonococcal complement-fixation test of the blood was negative. On the 12th day of the hospital admission sulphanilamide was started in daily amounts of 4 gm. On this treatment the arthritis subsided within 2 weeks and the local lesion was sterilized. On the 7th day after sulphanilamide she developed fever without an exacerbation of the arthritis which lasted 6 days and subsided. On the 18th day of treatment a maculopapular skin eruption appeared over the upper extremities. Following this, the drug was omitted. The gonococcal complement-fixation test became positive during the 4th week of observation. The skin eruption disappeared on the 2d day and she recovered completely.

In brief, this patient with gonococcal arthritis showed rapid and prompt improvement of the arthritis following treatment with sulphanilamide. The local focus was sterilized. Fever and a skin eruption appeared on the 7th and 18th days of treatment, respectively. The fever was self-limited in duration and disappeared in spite of the continuation of the drug. This case illustrates that sulphanilamide even in small doses may influence the course of arthritis favorably and sterilize the local focus. There is also evidence that the fever which follows the use of this drug may be self-limited in duration and, in some cases at least, disappear while the drug is continued.

Sulphanilamide in Synovial Fluid. Marshall, Emerson and Cutting⁴ have shown that when sulphanilamide is given by mouth it is readily absorbed into the circulating blood and diffuses through all of the tissues with more or less evenness. We have found that it diffuses into the synovial fluid so that the concentration in the fluid is practically the same as in the blood, although in 1 case we found it to be as high as 3 times that of the blood. This observation is helpful in understanding the reason that the synovial fluid may be sterilized with rapidity following the administration of the drug. That is to say, it appears that synovial fluid containing sulphanilamide will fail to support the growth of gonococci. In other work, we¹ have found that when the concentration of sulphanilamide is above 5 mg. % gonococci will not grow. Whether or not they are killed or die seems to depend somewhat upon the type of culture medium. It is perhaps well to recall that when the culture medium is changed so that organisms cannot reproduce, they frequently die, so that it is not possible to draw a sharp line between a bacteriostatic and a bactericidal effect *in vitro*. Table 2 shows the values of sulphanilamide in the blood and synovial fluid at the same time in 4 different patients.

TABLE 2.—COMPARISON OF SULPHANILAMIDE LEVEL IN THE BLOOD AND SYNOVIAL FLUID.

Patient.	Blood sulphanilamide, mg. per 100 cc.	Synovial fluid sulphanilamide, mg. per 100 cc.
1	5.9	5.7
2	8.2	7.7
3	5.1	4.1
4	2.3	1.9
5	5.8	6.1
6	6.2	18.8

From previous experience with infected synovial fluids, we have been unable to sterilize the fluid as quickly by any other means, so that it would seem advisable to give the drug so that the concentration in the blood and synovial fluid is at least 5 mg. per 100 cc.

Cellular Reaction in Synovial Fluid Following Sulphanilamide. It has been noted frequently by us⁵ that the total cell count is often higher in infected fluid than it is in sterile specimens. Moreover, as the patients improve, the total cell count diminishes and the neutrophils become less numerous. McEwen³ has found that following the aspiration of the knee joint there may be a temporary increase in the total number of cells in the synovial fluid; later as improvement occurs the number of cells decline.

When the knee joints of our patients were aspirated repeatedly and the cell counts followed before and after sulphanilamide, it was found that following the first aspiration there frequently was an increase in the total cell count but, as the fluid became sterile, the cells diminished rapidly in number; or, if it were sterile at the beginning, the number of cells per cubic millimeter diminished with improvement. The results in 9 cases are shown in Table 3.

These data tend to show that the intensity of the inflammatory reaction is reduced following sulphanilamide, and this may be taken as a favorable sign of improvement.

The Effect of Sulphanilamide on the Local Infection in the Genito-urinary Tract. It is now known that following sulphanilamide by mouth, profound changes may occur in some cases of gonococcal urethritis. In about one-half the cases the clinical signs of infection disappear and the local focus is sterilized. In other cases, the clinical signs of the infection disappear but the organisms remain in the local focus in spite of the use of sulphanilamide. These latter cases serve to emphasize the importance of the local body defense mechanism in the final destruction of organisms in most if not in all cases. Moreover, it is of the highest importance that these cases be recognized since these latent infections may be the cause of spreading the disease to others.

In the 14 cases of arthritis studied, the primary focus was determined in 11. In 2 of the remaining 3 cases the organisms were isolated from the synovial fluid and, in the final case, the clinical course

and the serological test justified the diagnosis. Of the 11 cases, in which the primary focus was determined by culture of urethral or cervical exudates, 8 were sterilized before they left the hospital

TABLE 3.—SUMMARY OF SYNOVIAL FLUID EXAMINATIONS BEFORE AND AFTER SULPHANILAMIDE.

Case.		Total cell count.	Culture.	Gonococcal complement-fixation test.	Sulphanilamide, mg. per 100 cc.	
					Blood.	Synovial fluid.
1	Before sulphanilamide	13,700	+	+	—	—
	After sulphanilamide					
	4th day	21,600	—	+	5.9	5.7
	7th day	16,000	—	+	8.2	7.7
2	Before sulphanilamide	80,000	—	+	—	—
	After sulphanilamide					
	2d day	51,000	—	+	5.1	4.1
	15th day	19,800	—	+	2.3	1.9
3	Before sulphanilamide	10,000	—	±	—	—
	After sulphanilamide					
	3d day	3,350	—	+	5.8	6.1
4	Before sulphanilamide	20,000	—	—	—	—
	After sulphanilamide					
	3d day	57,000	—	+	6.2	18.8
5	Before sulphanilamide	37,500	+	—		
	After sulphanilamide					
	3d day	45,000	—	—		
	5th day	26,000	—	±		
	8th day	11,500	—	+		
6	Before sulphanilamide	23,000	+	—		
	After sulphanilamide					
	4th day	37,500	—	+		
	6th day	25,350	—	+		
	8th day	20,000	—	+		
7	Before sulphanilamide	24,000	+	—		
	After sulphanilamide					
	10th day	20,000	—	+		
8	Before sulphanilamide	57,500	—	—		
	After sulphanilamide					
	3d day	57,000	—	—		
	7th day	80,000	+	—		
	9th day	85,000	+	—		
	11th day	85,000	—	—		
	15th day	70,000	—	—		
	17th day	60,000	—	—		
	19th day	55,000	—	—		
	25th day	50,000	—	—		
	32d day	50,000	—	—		
	39th day	40,000	—	—		
	51st day	15,000	—	—		
9	Before sulphanilamide	9,000	—	+		
	After sulphanilamide					
	5th day	11,000	—	+		

by the use of sulphanilamide alone. In 2 it was not possible to sterilize the local focus and, in 1, the patient left the hospital before the studies could be completed. These observations serve to indicate that it has not been possible in all cases to sterilize local foci of infection in the genito-urinary tract with sulphanilamide alone. This would suggest that the final destruction of the organism, in some cases at least, is due to the defense mechanism of the body.

Recurrence of Arthritis or Urethritis Following Withdrawal of the Drug. One of the conspicuous features in several of the cases was the recurrence of the arthritis following the withdrawal of the drug. In 1 patient this occurred on 2 occasions, and in another it was observed once.

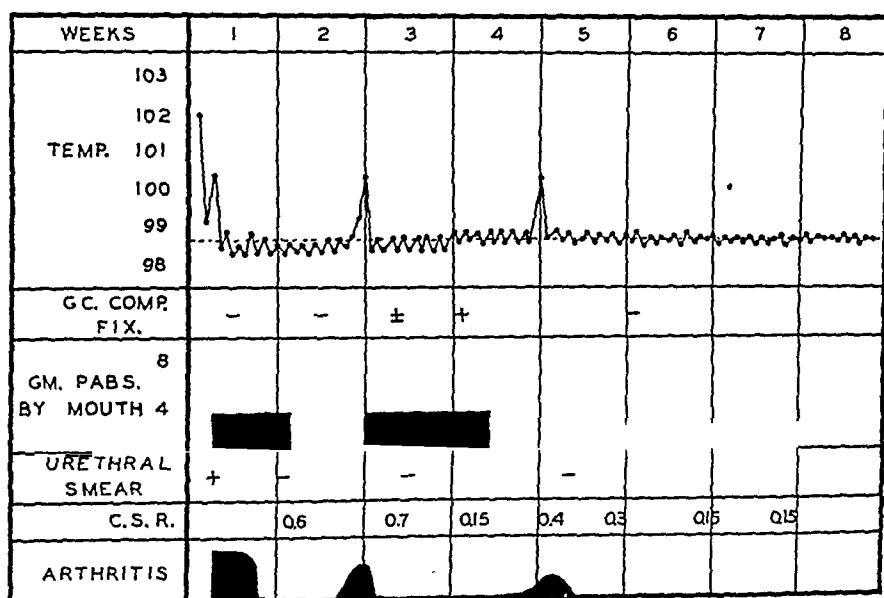


FIG. 4.—Patient with gonococcal arthritis treated with sulphanilamide. The local lesion was sterilized in 5 days. Two exacerbations of the arthritis with fever, following withdrawal of drug. Gonococcal complement-fixation test positive 16th day of observation. Sedimentation rate increased with increase in joint symptoms.

The course of events is shown for one of these cases in Figure 4. It can be seen that the temperature had returned to normal, the urethral exudate no longer contained gonococci, and the symptoms of arthritis had disappeared. The complement-fixation reaction, however, was negative and the corrected sedimentation rate was still elevated when the drug was withdrawn the first time. Five days after the drug was withdrawn, fever returned and there was an exacerbation of the arthritis. When the drug was readministered the arthritis and fever again disappeared. Ten days later, when the complement-fixation reaction was positive and the corrected sedimentation rate was normal, the drug was again withdrawn. Within 4 days there was another exacerbation of the fever and arthritis, and the sedimentation rate increased once again. All of these features disappeared following sulphanilamide.

A somewhat similar case is shown in Figure 2. Here there was fever and an exacerbation of the arthritis within 3 days after the withdrawal of the drug. It will be noted that the corrected sedimentation rate was still elevated above normal at the time of the examination.

In other cases, the continuation of the fever during the administration of the drug, even when the local infection of the urethra seems to be improving, may be due to an active infection in the joints which has not been adequately controlled. Figure 5 is an example of such a case and, since it illustrates several points, it requires comment.

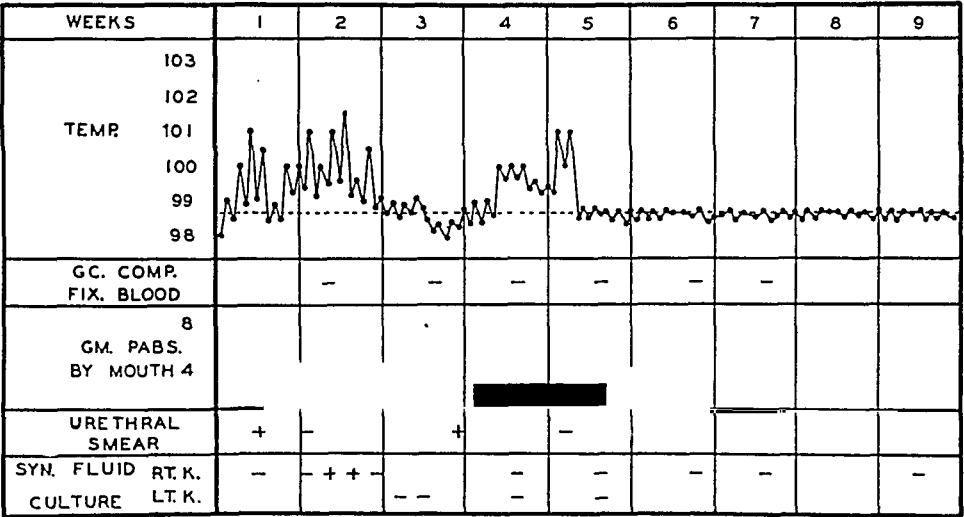


FIG. 5.—Gonococcal arthritis with recurrent effusions of fluid into the joints, a poor antibody response and an exacerbation of urethritis following the withdrawal of sulphanilamide.

A young colored boy with acute gonococcal urethritis and arthritis was given sulphanilamide by mouth for 2 weeks. The fever continued during this period although it tended to approach normal. During this time the urethral discharge became scanty and gonococci were not recovered from it. The synovial fluid from the right knee, which was at first sterile, became infected and the left knee became involved. When the drug was discontinued for 3 days, the urethral discharge again contained organisms and then disappeared when the drug was again started. When the drug was commenced a second time, there was an exacerbation of fever which was difficult to interpret. However, the effusion into the joints continued to recur. One important feature of the case was the failure of the patient to develop an immune response to the infection insofar as complement fixation antibodies were concerned.

This case served to emphasize that sterile fluid may continue to reaccumulate in the joints following sulphanilamide, that there may be an exacerbation of the urethritis following its withdrawal, and that the synovial fluid may contain gonococci during the time of its administration. Unfortunately, we do not have exact informa-

tion concerning the amount of sulphanilamide in the synovial fluid, but it is impressive that this patient never developed a positive complement-fixation reaction, suggesting at least that this patient had a poor or, at best, a slow immune response to the infection, and that this poor response on the part of the patient was responsible for the prolonged course of the disease.

Side Effects. Four of the 14 patients showed the side effects of the drug. One patient developed hemolytic anemia, 2 showed febrile reactions with a rash, and 1 had fever without any other signs of intoxication. Practically all of the patients were cyanotic; 1 had nausea, vomiting, and diarrhea; and all of them were somewhat depressed and complained of weakness while they were taking the drug.

The patient who developed the hemolytic anemia recovered promptly following blood transfusion, forcing of fluids, and cessation of the drug. In the individuals who developed fever and skin eruptions there was a prompt recovery following the withdrawal of the chemical. There is some evidence that leads one to believe that the febrile reactions are self-limited in extent since they disappear even when the drug is continued after fever reappears.

The various side effects of the drug have been amply discussed elsewhere and they need not be repeated at this time. It is well to emphasize, however, that the most alarming reactions are hemolytic anemia, agranulocytosis, and the febrile reactions with or without skin eruptions.

Comment. From the results in the 14 cases it seems fair to say that sulphanilamide in adequate dosage affects the course of gonococcal arthritis in a striking manner. In order to accomplish the best results it is necessary to increase the concentration of the drug to at least 5 mg. % or higher in the circulating blood and synovial fluid. This can usually be done by giving 4 or 5 grams (60-75 grains) a day in divided doses. Since there is some variation from one patient to another in the rapidity with which they absorb and maintain the sulphanilamide level in their blood, it is necessary to check the blood level every 2 days during treatment. In the patients with sterile synovial fluid there is evidence that the cell count diminishes and the fluid reaccumulates less rapidly after its administration, and the duration of the illness is shortened. When this level is reached, the growth of organisms in the synovial fluid is inhibited and it becomes sterile. Moreover, there is often a profound effect on the local focus in the genito-urinary tract so that it is sterilized much sooner than frequently happens during the natural history of the disease.

The studies of the action of sulphanilamide *in vitro* on the gonococcus would indicate that it inhibits the growth of the organism in whole blood or in other media and, when the concentration is

adequate, organisms fail to survive. When it is given to patients with gonococcal infection it would appear to exert a profound inhibitory effect on the growth of the organism but it does not cause sterilization of foci of infection in all cases. Moreover, when the drug is withdrawn, there is often a recurrence or exacerbation of the signs of infection. These observations suggest that the normal defense mechanism of the body plays a marked rôle in the final destruction of the organism in the host. For the optimum results, then, one should have a sufficient concentration of the drug in contact with the organisms and a defense mechanism that is capable of destroying organisms.

From the results that we have observed in this small group of cases, it is fair to say that the results are encouraging and that all patients with gonococcal arthritis should be treated intensively with the drug.

Summary and Conclusions. From a study of 14 patients with gonococcal arthritis who were treated with sulphanilamide the following facts emerged.

1. Sulphanilamide has a striking effect on the growth of the gonococcus *in vitro* and *in vivo*. To produce the optimum effect it is necessary to have a concentration of 5 or more mg. per 100 cc. in the blood.

2. The drug diffuses into the synovial fluid and is present in approximately the same concentration as it exists in the blood.

3. The infected synovial fluid is sterilized within several days after the drug is administered, provided the concentration is adequate.

4. Recurrences of the arthritis, fever, and the urethritis may follow the withdrawal of the drug. It is well to continue its use until the sedimentation rate is normal and, if the complement-fixation reaction has been negative, it should be continued until it is positive.

5. The most striking results were obtained in patients with infected synovial fluid.

6. There is some evidence that the body defense mechanism is of importance in ridding the body of organisms.

7. The side effects are of sufficient frequency so that all patients who are receiving the drug should be followed with care.

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CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS.

V. CLINICAL EVALUATION OF CARDIODYNAMIC STUDIES.*

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IN evaluating the condition of the circulation, it must be stressed that a single look on the clinical state of the patient often tells more than many painstaking tests devised to measure the efficiency of the circulatory apparatus. This is largely because the look is "correlative"—the patient is seen as a whole. If a quantitative measure of the circulation is desired, however, the circulatory apparatus must be divided into several components or aspects—the volume circulated, the speed of circulation, the pressure, and so on, divisions that depend arbitrarily on the scientific methods available for quantitative assay of the circulation. Thus the important components that can be measured without too great difficulty are circulating blood volume, cardiac output, circulation time, venous pressure, blood pressure and cardiac rate. In order to integrate and correlate the different components of the circulation to give a better evaluation in any particular patient a schema for showing the relationship between the important factors maintaining circulatory equilibrium has been devised (Fig. 1).

Reference to the figure shows that the total amount of blood in the body available for circulation is of two kinds, one actively circulating, and the other slowly circulating, stored blood—the important storage organs or blood depots being the liver, spleen, lungs, skin, muscles and splanchnics. The total volume of actively circulating blood makes one round of the circulation in a *revolution period*. The length of the revolution period varies directly with the *volume of blood* that is circulating and inversely with the *rate of the heart* and the amount of blood pumped out by the heart with each stroke (*stroke volume*). Perhaps the most important factor influencing the rate of the heart and thus indirectly the size of the cardiac stroke is the volume of blood returned to the right auricle, the venous return, which depends directly on the venous pressure.

* This study was made possible by the fund generously established for this purpose by Mr. Henry Dazian.

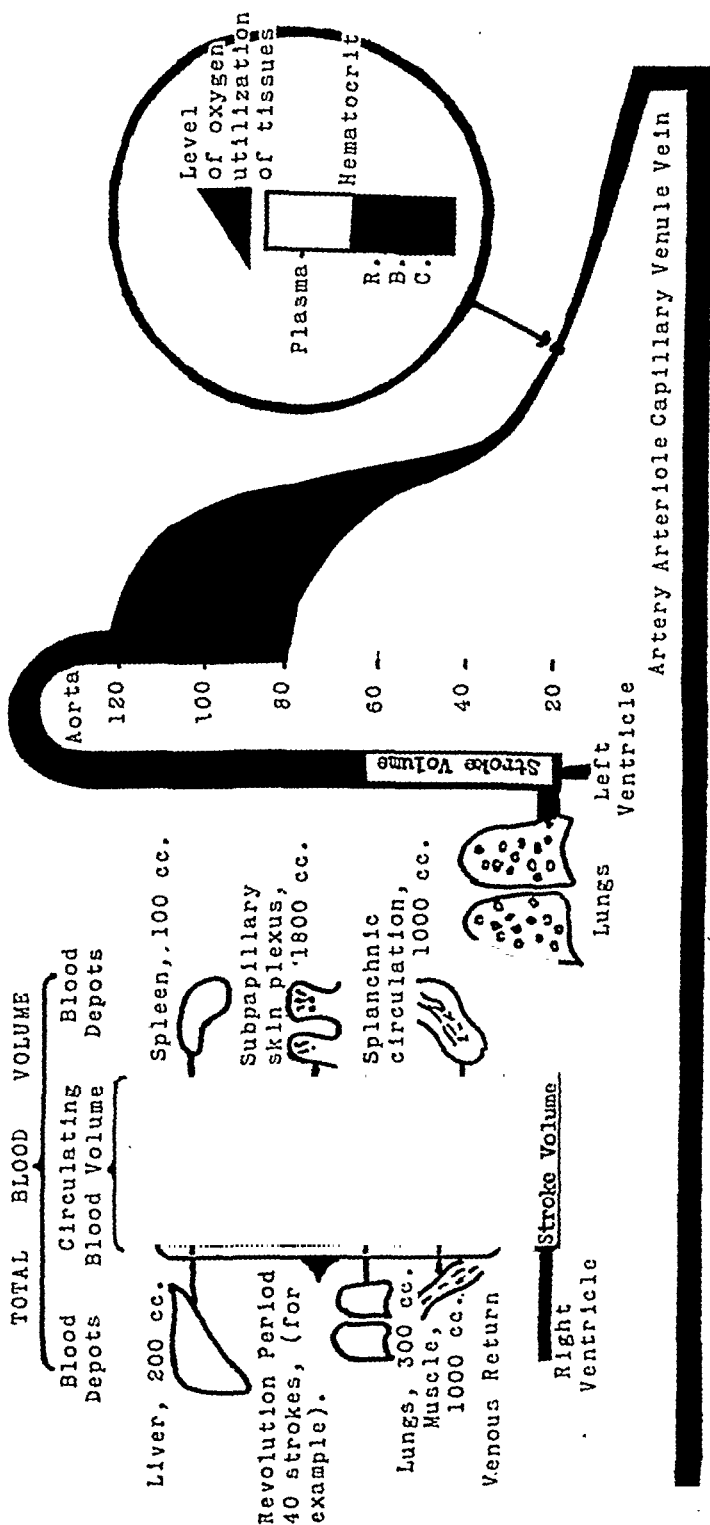


FIG. 1.—Schema showing relationship of factors maintaining circulatory equilibrium.

The schema further represents the blood as circulating through the lungs, where it becomes oxygenated, and is returned to the left ventricle, the important pumping station that must impress the proper "head of pressure" on the blood pumped into the systemic circulation. This "head of pressure" falls slowly through the arterial branches, and very rapidly through the arterioles and capillaries before it reaches the tissues. From the tissues the blood collects in venules and larger veins to be returned to the right heart at a rate determined by the venous pressure.

It is unfortunately impossible to measure with exactness the revolution period (the average time it takes for the whole body of actively circulating blood to make the round of the circulation), since there are so many varied pathways the blood may take, and since there is such great variation of the speed of different parts of the blood in the same blood-vessels, *i. e.*, faster in the central stream, slower on the sides. The closest approach to the desideratum possible with our present-day methods is to measure the time for the *fastest moving* particles to traverse a definite circuit. This is called *circulation time*, and is designated by the names of the two points which mark the beginning and end of the circuit—vein to lung circulation time, and so on. Figure 2 was drawn to show (among other things) the different circuits used today in measuring the speed of circulation. A more detailed consideration will be taken up in the section dealing with circulation time.

We now turn to a consideration of the methods used to determine these different components of the circulation so that we can finally attempt a clinical evaluation of their usefulness.

Blood Volume. It has been shown experimentally (Barcroft¹ and others) that the total amount of blood in the body does not circulate with the same speed through all the organs. There are some in which the blood circulates rapidly, actively, while in others, such as the spleen and liver, the circulation is very much slower, making of these latter organs a sort of reservoir where the blood is stored rather than actively circulated. *These organs which are able to store blood and release it to the circulation when needed without detriment to the organ or any other part of the body are called blood depots.** The exact mechanism by which the blood is stored and later given up to the active circulation concerns us in that it helps clarify the nature of the blood depots.

In the spleen the blood appears to be *shunted* into the numerous venous sinuses. The hoarding and discharging of blood is regulated largely by the vegetative nervous system (Rein¹²). Stimulation of the vagus system causes the spleen to hoard blood, while with sympathetic stimulation (as with increase of adrenalin in the blood),

* Figure 1 shows the important blood depots and the amount of blood they are capable of releasing into active circulation (estimated, not measured). Note that the amount of stored blood is almost equal to the circulating blood volume.

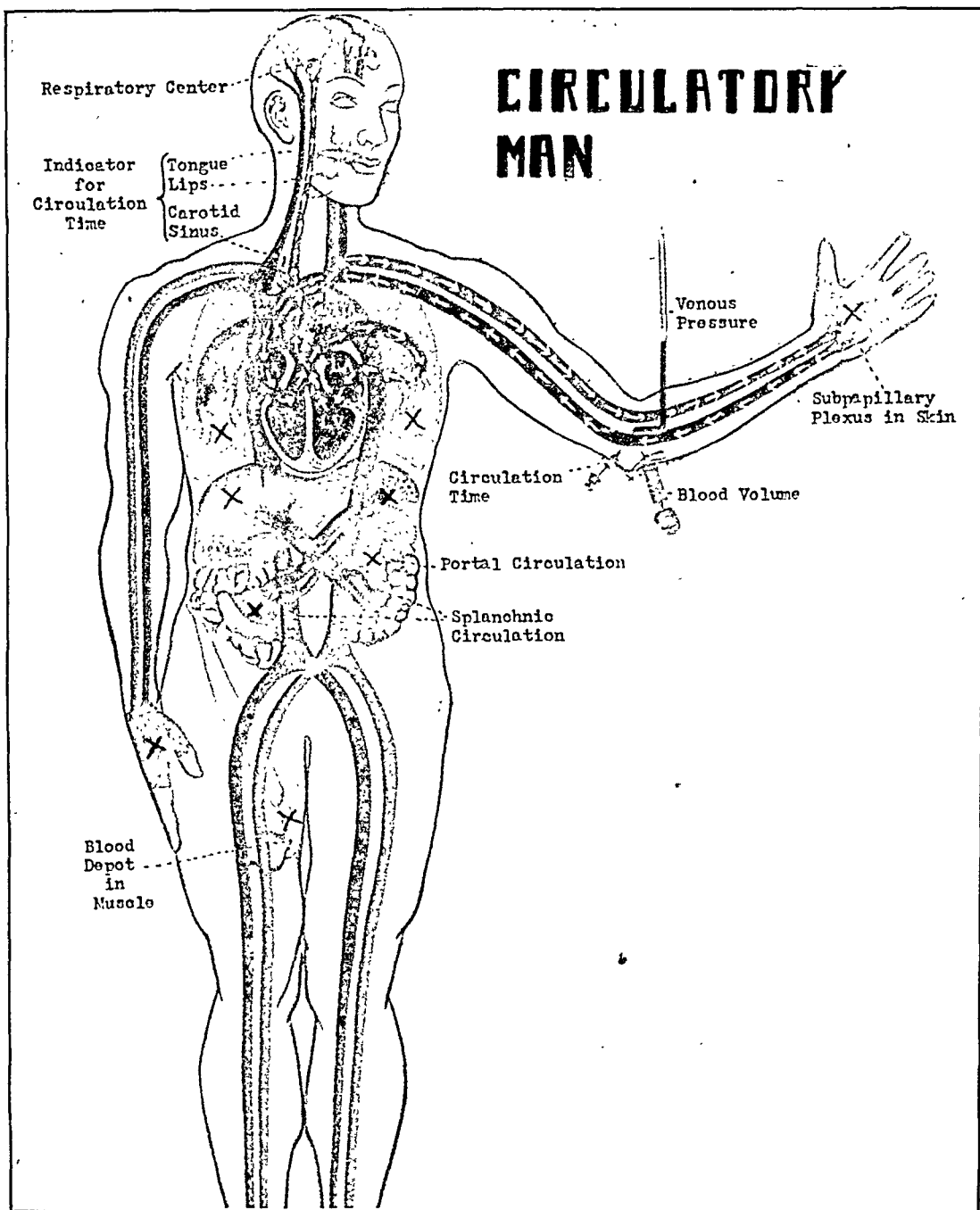


FIG. 2.—Circulatory man—a diagrammatic representation of the cardiovascular apparatus and blood depots. (See text for fuller discussion.)

the spleen contracts and the greater part of the stored blood (as much as 100 cc.) is pushed into the circulation.

In the liver, Mautner and Pick¹¹ believe there is a *throttle* mechanism exerted by the muscular walls of the central veins which dams up the blood and then discharges it (about 200 cc.) into the circulation in time of need.

Wollheim¹⁷ has shown that in the venous bed of the splanchnic system and the subpapillary plexus of the skin, storage of blood is mediated through a *blockage* process whereby a large quantity of blood is absorbed from the circulation through small vascular apertures; and that vasoconstriction empties as much as 1800 cc. quickly into active circulation.

We agree with Hochrein and Keller,⁷ that the lungs may also be said to be blood depots which, by change in their volume (due to differences in position of the diaphragm and the ribs), are able to contribute an appreciable amount of blood to the circulation (about 300 cc.).

From the clinical point of view, when we speak of blood volume we are concerned only with the actively circulating and not the stored blood. By definition *circulation blood volume is the total amount of blood moving actively and rapidly through the circulation.*

In determining blood volume 10 cc. of an easily diffusible, non-toxic dye (0.6% trypan red) is injected into one antecubital vein according to a modification of the method of Keith, Rowntree and Geraghty.⁸ The dye diffuses readily and becomes uniformly diluted by the blood plasma within several minutes (the red blood cells absorbing only a negligibly small fraction of it). Samples of blood are taken 3 and 6 minutes after injection, before any appreciable part of the dye is removed from the circulation by the reticulo-endothelial system. The dye has been diluted about 500 times in the circulating plasma, the exact degree of dilution being determined by comparing the imparted color of the plasma withdrawn with a standard containing a known dilution of the dye. This indicates how much plasma was present in active circulation to accomplish the dilution. The figure obtained is the total *plasma volume*. To determine total blood volume one must know what percentage of the patient's blood is plasma, and what percentage is cells. The latter, the *hematocrit reading*, is determined by centrifuging a small sample of the patient's blood in a thin graduated tube $\frac{1}{2}$ hour at 10,000 revolutions a minute, and reading off directly on the tube the percentage of packed cells.

With the trypan red method we⁴ have found the plasma volume in the normal to vary between 36 and 49 cc. per kg. body weight (average 40.5), and the total circulating blood volume from 66 to 90 cc. per kg. (av., 78.4). The hematocrit varied from 36.5 to 50.5% (av., 43.8%). The total plasma volume averaged 2780 cc.; the

total circulating blood volume, 5386; the average circulating blood volume per square meter of surface area was 3037 cc.

There are certain physiologic factors that have been shown to influence the circulating blood volume. Of those which increase the blood volume one must mention exercise, low atmospheric (oxygen) pressure, inhalation of carbon dioxide, administration of epinephrin, caffeine, pituitrin or thyroid substance. Some of the more important factors causing a decrease of the blood volume are sleep, postoperative shock, high atmospheric (oxygen) pressure, diets poor in salts and nitrogen, and drugs like digitalis, histamine and morphine. The changes in blood volume which occur in various pathologic conditions will be discussed later with the clinical evaluation of the usefulness of this method.

Cardiac Output. Perhaps more important than the knowledge of the total amount of blood available in the organism is the determination of how efficient the heart is as a *pump* keeping the blood circulating, *i. e.*, how fast the heart is beating, and how much it is expelling with each beat. The first is arrived at very easily by listening to and counting the heart sounds—the second, stroke volume (and cardiac output) is determined with much greater difficulty.

The cardiac output is defined as *the amount of blood pumped out by the ventricle into the periphery, expressed in terms of liters per minute. The amount ejected with each systole is called the cardiac stroke, systolic output, or stroke volume, and is evidently the cardiac output divided by the heart rate.*

The Grollman method in general use now for the determination of cardiac output is based on the principle that blood flowing through the lungs enters into equilibrium with a foreign gas that is inhaled. If the solubility of the gas in blood is known, and one determines how much gas has been absorbed by the pulmonary blood during a unit of time, one can calculate the amount of blood flowing through the lungs that accomplished this absorption. Since the amount of blood flowing through the lungs is the same as the amount flowing through the heart, the method measures cardiac output indirectly.

The efficiency of the heart as a pump depends not only upon the amount of blood but upon the concentration of oxygen in the arterial, as compared with the venous blood. An efficient circulation maintains a high *arteriovenous oxygen difference*, defined as *the number of cc. of oxygen given up to the tissues by a liter of blood.* Furthermore, the oxygenation of the tissues is not only a function of the lungs and blood, but depends also upon the individual tissue activity. *The ability to utilize the oxygen brought to the tissues is called the oxygen utilization*, and is calculated as the arteriovenous oxygen difference divided by the total oxygen content of the arterial blood.

The Grollman method of determining cardiac output using acetylene as the foreign gas need not be detailed here; his monograph covers this subject adequately.⁵ In essence the method requires the breathing from a bag of a gas mixture containing about 25% acetylene until it comes into equilibrium with the pulmonary blood (about 6 cycles of inspiration and expiration), then taking a sample of the mixture in the lung-bag system. After 3 more cycles another sample of alveolar air is collected. When the oxygen, carbon dioxide and acetylene in the 2 samples are analyzed in a Haldane apparatus, sufficient data are obtained for cardiac output determination, if the basal metabolism is known.

Using a modification of the Grollman method in 50 cases, we^{2c} have found the cardiac output in normals to vary between 3.24 and 4.38, the average being 3.96 liters per minute. The stroke volume varied between 42 and 63 cc. with an average of 54 cc. If a less variable and more scientifically correct figure is desired, the results should be expressed in relationship to the surface area. This figure, the *cardiac index*, is the *cardiac output divided by body surface area*, and in the normal varied from 2 to 2.43, the average being 2.23 liters. The arteriovenous oxygen difference ranged from 49 to 63 cc. and averaged about 53 cc.

It is to be noted that cardiac output in its intimate relationship to oxygenation of the tissues is so fundamental a function of the body that it can be calculated for the normal individual and found to coincide with the measured values as closely as the basal metabolism can be calculated for the normal. The findings in abnormal cases will be discussed later in the second part of this article.

Venous Pressure. An important factor in the circulation is the pressure of the blood returning to the heart. By the Bainbridge reflex discussed before, an increase in venous pressure causes an increase in cardiac rate and is therefore important in regulating cardiac output. *The venous pressure may be defined as the residue of pressure in the venous side after the resistance in the arteries, arterioles, capillaries and venules has been overcome.* There are many factors affecting the venous pressure aside from the efficiency of the heart in maintaining the vis-a-tergo. Extracardiac factors are found all along the course of the veins—the contraction of the muscles in which the veins are embedded, the intra-abdominal pressure, changes in intrapulmonary pressure due to inspiration and expiration, the competency of the venous valves, and so on. There are also localized conditions, such as mediastinal tumor or aneurysm which cause an increase in venous pressure (usually unilateral).

A reliable way of determining venous pressure is the direct method of Taylor, Thomas and Schleiter,¹⁶ which simply calls for venipuncture of the antecubital vein, the arm being held at the mid-level of the right auricle and the needle connected to an L-shaped hollow tube. The level that the blood rises to indicates the venous pressure

directly in centimeters. In our normal cases³ the venous pressure figures ranged between 4.2 and 7.8 cm. (av., 5.36 cm.). The importance of increased venous pressure clinically will be discussed later.

Circulation Time. Aside from knowing the amount of blood available for circulation and the amount pumped out by the heart in a unit of time, one would like to know the velocity of blood flow. The speed of flow is evidently very variable, the mean velocity in the aorta being probably close to 50 cm. per second, in the capillaries possibly only 0.5 mm. per second, and again in the large veins about 15 cm. per second. There are so many available avenues of flow for the blood that it is impossible to test with exactness the total mean velocity. However, if comparative figures only are desired, one could determine the speed of blood flow in a characteristic circuit. A convenient one that is most often chosen for this is the vein-to-head circuit (Fig. 2). In the majority of our cases we have used the cyanide method proposed by Robb and Weiss¹³ for the determination of pulmonary circulation time. Sodium cyanide solution, 0.25 cc. of 3%, is injected into the antecubital vein. As Figure 2 shows, the cyanide is carried through the right heart and lungs back to the left heart to be finally ejected into the systemic circulation. The first appreciable quantity of cyanide reaching the carotid sinus sets up a reflex respiratory stimulation which causes the patient to take a few deep breaths. The time interval between injection and the first signs of respiratory stimulation marks *the time it took for the fastest moving foreign particle to traverse the circulation between the two chosen points, peripheral vein and neck*. This is the circulation time between these two points, and is usually designated as *pulmonary circulation time*.

It depends upon the substance used as to what the circulation time will be. Thus, if instead of cyanide, 0.3 cc. of ether is injected into the antecubital vein, as suggested by Hitzig,⁶ it will go through the right heart and into the lungs where the odor of ether would be detected as soon as this highly volatile substance reached the pulmonary arterioles (and capillaries). The circulation time determined in this manner is shorter, since it measures the speed through the right heart circuit only. The speed through the left heart circuit can be obtained by subtracting the vein-lung ether time from the vein-head cyanide time (Fig. 2).

The average circulation time from arm to head by the cyanide method in our normal cases⁴ is 12 to 21 seconds (av., 16 seconds). The arm-to-lung time (right heart circuit) is 3.5 to 8 seconds (av., 6 seconds).⁶ The circulation time for the left heart circuit is therefore 16 minus 6, or about 10 seconds average. The clinical significance of variations from the normal figures will be discussed later.

Clinical Evaluation. In evaluating the clinical usefulness of the cardiodynamic studies outlined above, one must draw a distinction between the use made of the fundamental experimental studies in

laying the physiologic basis for our concept of certain clinical diseases, especially cardiac, and the present-day application of the methods in the study of a patient. Historically we owe a great debt to these studies in helping us explain the essential disturbances in a great many clinical disorders, even if it is no longer important to reaffirm these relationships when confronted with a similar case in our clinical practice.

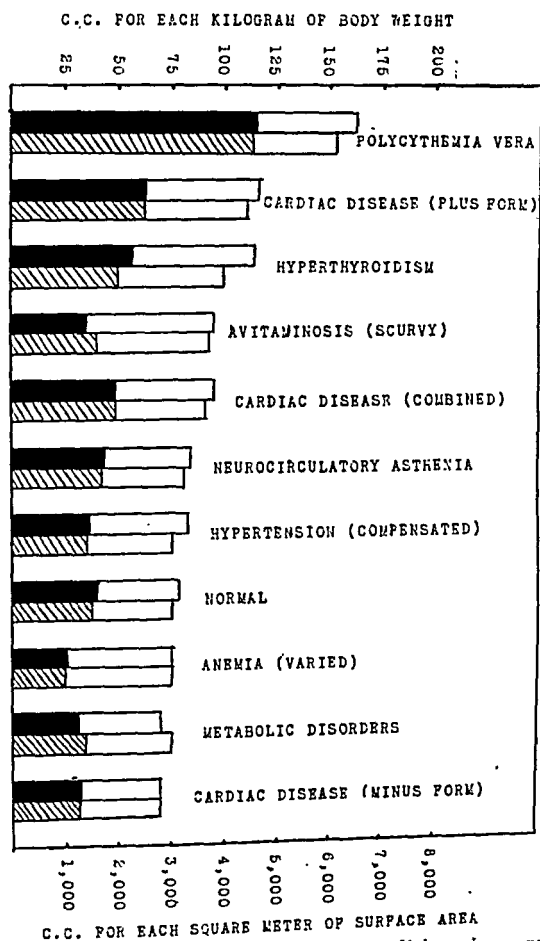


FIG. 3.—The circulating blood volume in varied conditions is represented by the total height of the columns; the solid column indicating the blood volume for each kilogram of body weight, and the cross-hatched the blood volume for each square meter of surface area. The clear area of each column represents the plasma volume.

In hypertension, for example, the marked elevation in blood pressure had led us to expect marked changes in the other cardio-dynamic factors which help maintain the circulatory equilibrium. But the actual measurements of these factors (which our work corroborates)* show that aside from a very slight increase in oxygen

* Demonstrated by the authors in an exhibit on the Cardio-dynamic Factors in Hypertension at the Scientific Fortnight, the Academy of Medicine, November 1 to 12, 1937.

consumption and a concomitantly small increase in cardiac output (an average of 4.46 liters where the normal is 3.96), there is no significant change in the circulation. Before decompensation sets in, hypertensives have normal blood volumes, venous pressures, circulation times and heart rates (Figs. 3, 4 and Table 2). There must evidently be some mechanism of compensatory dilatation of blood-vessels to negate the effect of increased peripheral resistance

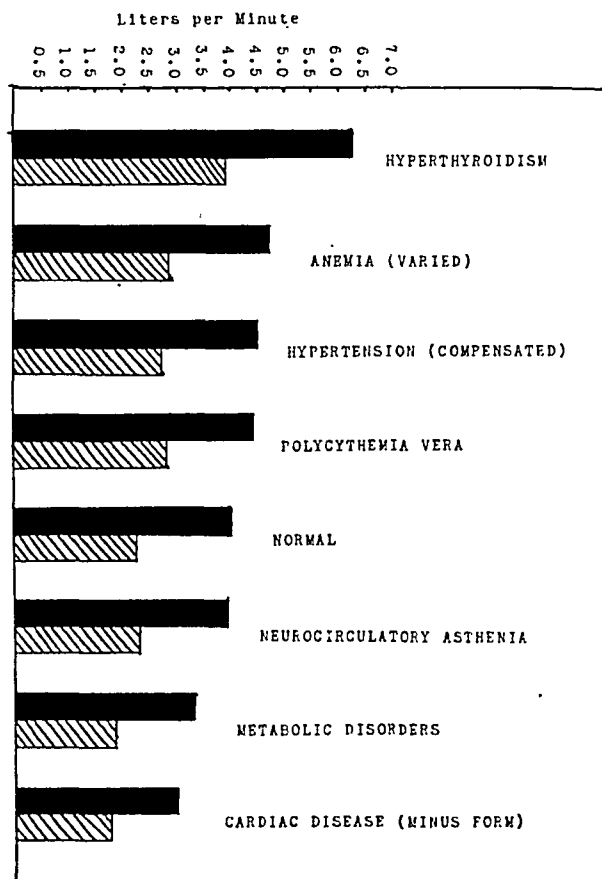


FIG. 4.—The solid columns indicate cardiac output in liters per minute. The cross-hatched columns represent cardiac output per square meter of body surface (cardiac index). The figure shows a more constant value for cardiac index, as compared to cardiac output.

on the circulation (Table 1, a summary of the cardiodynamic findings in the varied hypertensive states).

In these cases of essential hypertension, the decompensation which first sets in is typically that of left ventricular failure. The disturbance manifests itself mainly by pulmonary congestion because of the impeded pulmonary blood flow, the rigidity of the lungs and the diminution in the capacity of the alveolar spaces; clinically it

shows itself as decreased vital capacity, dyspnea, cyanosis and orthopnea. At first, while the failure is limited to the left side, there is no disturbance in the cardiodynamic factors, except for the circulation time. Due to the retardation of flow through the pulmonary circuit one will find a prolongation of the pulmonary circulation time (arm-to-head), while the time of circulation from the arm to the lung will still be normal.

TABLE 1.—TYPICAL CASES ILLUSTRATING THE CARDIODYNAMICS IN VARIED STATES OF HYPERTENSION.

Clinical case.	Sex.	Body weight, kg.	Body surf., sq. m.	Blood pressure, mm. Hg.		Plasma volume.		Blood volume.		Hematocrit, %	Arteriovenous oxygen difference.	Minute volume, liters.	Cardiac index.	Cardiac stroke, cc.	Circulation time (cyanide), sec.	Venous pressure, cm.
				Systolic.	Diastolic.	Cc. per kg. body weight.	Cc. per sq. m. body surf.	Cc. per kg. body weight.	Cc. per sq. m. body surface.							
Normal	M	57.2	1.62	110	70	42.3	1499	84.9	3000	45	62	3.24	2.0	42	17	4
Essential hyperten. plus decompensation	F	55.8	1.44	250	140	55.8	1922	148.2	5093	57	*	*	*	*	21	34
Hypert. coronary minus decompensation	M	82.0	1.89	200	130	33.0	1370	54.8	2715	36	60	3.28	1.7	46	..	5
Hypert. obesity, metabolic	M	92.7	1.97	210	75						84	3.36	1.7	42	13	8
Polycythemia vera	M	70.4	1.70	150	90						67	3.60	2.1	45	12	4
Hypert., compensated	M	71.8	1.71	205	120						50	4.60	2.7	47	16	7
Hyperthyroidism active	M	52.0	1.53	150	85						55	5.30	3.5	43	10	8

* Not determined because of orthopnea.

TABLE 2.—AVERAGE CARDIODYNAMIC VALUES IN VARIOUS CLINICAL CONDITIONS, SHOWING BLOOD PRESSURE, CIRCULATING BLOOD VOLUME, CARDIAC OUTPUT, VENOUS PRESSURE AND PULMONARY CIRCULATION TIME.

Clinical case.	Number studied.	Body weight, kg.	Body surface, sq. m.	Blood pressure, mm. Hg.		Blood volume.				Cardiac output.							Pulmonary circulation time (cyanide), sec.
				Systolic.	Diastolic.	Cc. plasma vol. per kg. wt.	Cc. plasma vol. per sq. m. surf.	Cc. total blood vol. per kg. wt.	Cc. total blood vol. per sq. m. surf.	Hematocrit, %.	Oxygen consumption per min.	Pulse.	Arteriovenous oxygen difference, cc.	Minute volume, liters.	Cardiac index.	Cardiac stroke, cc.	
Normal	10	68.7	1.76	110/70	40.5	1575	78.4	3037	43.8	228	72	57	3.96	2.23	54	4	16
Hyperthyroid	9	53.2	1.51	130/73	58.0	2023	114.2	3981	44.5	292	106	47	6.27	3.93	58	6	12
Neurocirc. asthenia	6	64.9	1.69	115/75	41.8	1591	84.4	3192	45.3	224	78	57	3.90	2.32	49	4	15
Cardiac disease:																	
Plus form	7	58.9	1.58							*	*	*	*	*	*	19	21
Minus form	15	68.5	1.72							222	91	72	3.08	1.81	34	12	25
Combined	22	61.6	1.65	159/94	45.1	1135										14	23
Hypertension compensated	5	61.0	1.60	190/103	44.0	1618	81.6	3020	42.4	258	84	58	4.46	2.62	53	8	13
Polycythemia vera	7	57.9	1.57	140/84	42.2	1571	167.7	6090	67.5	284	82	68	4.24	2.66	50	4	18
Anemia (varied)	6	63.1	1.60	124/74	49.8	1957	74.9	2938	30.0	249	77	54	4.63	2.76	60	8	13
Metabolic disorders	7	83.2	1.84	128/68	36.6	1589	69.3	2980	42.1	249	76	73	3.37	1.87	44	8	18
Avitaminosis	1	60.0	1.70	120/70	61.8	2180	95.3	3762	30.0								
Oblit. pul. arteritis	1	57.2	1.67	110/60	49.1	2813	91.4	5228	42.5	300						4	16

* Determinations not accurate because of orthopnea and marked dyspnea of patients.

If decompensation in the hypertensive progresses, both the right and left sides of the heart will show signs of failure. With beginning edema formation one notices a prolongation of both the arm-to-lung and arm-to-head circulation time. Most decompensated hypertensives show an increased circulating blood volume, an increased venous pressure and a normal or decreased cardiac output. They are of the dyspneic, orthopneic, cyanotic type with distended neck veins.

Infrequently one finds a hypertensive with a reduced blood volume. Such patients are not likely to be as dyspneic, orthopneic or cyanotic and present in many cases a different clinical aspect, especially from the therapeutic point of view. This has given the impetus for the classification of decompensated cardiacs into two general divisions, one with *increased blood volume*, such as decompensated hypertensives, called the *plus form* of decompensation; and the other with *decreased blood volume*, the *minus form*, of decompensation seen typically in recurrent endocarditis and recurrent rheumatic mitral conditions. In the minus form of decompensation the patient usually has a somewhat increased venous pressure, a normal circulation time and a low normal or decreased cardiac output. He does not require much propping up in bed.

The practical importance of the distinction between plus and minus forms of decompensation is in therapy. Certain drugs, such as morphine, are known to reduce blood volume and (other things being equal) they are therefore contraindicated in cases in which the blood volume is already reduced. Conversely, drugs like adrenalin, caffeine and pituitrin cause an increased blood volume, and are likewise contraindicated in the treatment of those heart failures connected with increased blood volume—the plus form of decompensation so common in hypertensives, and so on.

A further distinction that the classical studies of the cardiodynamic factors have helped clarify is that between central and peripheral failure. Peripheral failure is best exemplified by the condition of shock and collapse seen postoperatively, or in connection with injury or acute nervous disorders. The difficulty is essentially a failure of the return of venous blood from the periphery to the central pumping station, the heart. The peripheral constriction is accompanied by stagnation of blood in the dilated splanchnics. The circulating blood volume, the venous pressure and the cardiac output are all reduced. The heart must pump more frequently to receive the required amount of oxygen, a fact which explains the almost constant tachycardia. The state of shock or collapse is thus seen to be similar in many respects to the minus form of decompensation. The differentiation is very simple, however. In shock the splanchnic tone is not maintained, the venous pressure is zero, the blood pressure is low; while in the minus form

of decompensation the splanchnic tone is maintained without fall in blood pressure or venous pressure.

It is not suggested, of course, that if one has a clinical case of hypertension a complete cardiodynamic study should be made so as to better understand the patient's condition, or that a similar study should be made of a patient in shock. As mentioned above, the classic studies are of historic significance, and once established, they need no repetition. There are, however, certain clinical conditions where cardiodynamic studies are of present-day practical value.

For example, one of the most constant manifestations of beginning heart failure is increase in the venous pressure.³ The method of visualization of the neck veins that Lewis¹⁰ recommends may be sufficient to give one a rough estimate of the venous pressure, but where this would be most useful (*i. e.*, as the only definite sign in incipient cardiac failure), a more accurate method, such as the direct venipuncture detailed in the earlier section should be used. Figures above 8 cm. which are not due to extracardiac factors indicate circulatory embarrassment (Table 2, which shows an average venous pressure of 12 in the minus form of cardiac decompensation and of 19 in the plus form).

Although it is not often useful to differentiate decompensation into failure of the left or of the right heart because pure failure of either type is infrequently encountered clinically, there are occasions in which this differentiation is of importance. This is particularly true when we know the natural sequence of failure in certain clinical conditions—that left-sided failure in hypertension precedes and progresses to right-sided involvement also. It is then very much worth while to do the circulation time by two methods, one which will show the arm-to-lung time (the right heart), the other, the arm-to-head time representing the speed of circulation through right and left hearts. A subtraction of the first from the second time gives a fair idea of the relative speed of the two heart circuits. Although this subtraction does not yield figures that are absolutely diagnostic (since there is such variation in the normal limits of circulation time), an approximate idea of the speed through the heart and lungs can be obtained.

There is another condition in which we have found the cardiodynamic studies of definite clinical value and have recently reported upon this.^{2b} Clinically cases are encountered which closely simulate hyperthyroidism but which are in truth neurocirculatory asthenia or incipient tuberculosis (especially in asthenic individuals with labile vasomotor systems). In many of these non-thyroid cases, as Lahey⁹ has reported, the basal metabolic rate is raised to as high as 40 or 50, so that the B.M.R. cannot be relied upon in a diagnosis of borderline thyrotoxicosis. A more reliable indication of hyperthyroidism is the altered cardiodynamics. We have found in our

true hyperthyroid cases a markedly increased cardiac output, increased blood volume and increased speed of circulation (Figs. 3, 4 and Table 2). In the metabolism of the hyperthyroid individual, in spite of increased oxygen consumption, there is a diminished utilization of oxygen by the tissues, expressed by a diminished arteriovenous oxygen difference. From the formula cardiac output = $\frac{\text{oxygen consumption}}{\text{a-v oxygen difference}}$ we see we must have an increased cardiac output. In fact, the cardiac output in hyperthyroidism averages about 6.27 liters, as compared to the normal of 3.96 liters. The blood volume too is raised to an average of 114 cc. per kg., where the normal is 78.4 cc. per kg. The circulation time is usually reduced from the 16 seconds normal to about 10 seconds, because of the need for active, rapid circulation. This helps compensate for the reduced power of the tissues to utilize the oxygen brought to them, reflected by the diminished arteriovenous oxygen difference (av., 47 cc.). In contrast to the above, we note that in cases of neurocirculatory asthenia or incipient tuberculosis, the diseases not being metabolic, the cardiodynamic factors remain normal. Although they may have an increased oxygen consumption there is no change in the other factors. We feel then that cardiodynamic studies are of definite aid in the clinical differentiation of borderline hyperthyroid cases, and that if the facilities for doing the cardiac output are not present, at least circulation time and blood volume determinations should be made.

We have further had the occasion to utilize the cardiodynamic studies in an unusual case of obliterating pulmonary arteritis which closely resembled thyrotoxicosis clinically (*i. e.*, B.M.R. was +37).¹⁴ The perfectly normal blood volume and circulation time helped rule out the possibility of hyperthyroidism (Table 2).

As reference to Table 2 would show, perhaps the most important clinical use of blood volume studies is in the diagnosis of polycythemia. Even clinically it is difficult at times to differentiate the polycythemia vera from the symptomatic. Their natures, of course, are entirely different; the true polycythemia being a hyperplastic blood disease, and the symptomatic a manifestation of difficulty of aëration, stagnation and hypertension in the pulmonary circuit. In true polycythemia we get the very highest blood volume and hematocrit readings. *The hematocrit is at least as important as the increase in blood volume.* We must demonstrate that the increased blood volume is not due to any appreciable increase in plasma, but to increase in the cellular content of the blood before we can call it a true polycythemia. Thus with blood volume above 7000 total (4300 cc. per sq. m. of body surface), and hematocrit readings above 55%, we know we are dealing with a polycythemia vera. The symptomatic polycythemias fall below these figures (Table 2).

It is interesting to note that in spite of the increased blood volume

in polycythemia there are no other disturbances in the cardiodynamic factors except for a slightly prolonged circulation time.* The increased viscosity of the blood evidently produces a slower blood flow. The cardiac output remains normal, but it takes the blood longer to make one complete revolution, *i. e.*, there is prolongation of the "*revolution time*."^{2a}

It is of great importance to do a total blood volume and hematocrit reading in cases of polycythemia vera. For clinical purposes, if the facilities for the former are not present, at least the hematocrit reading should be obtained.

Summary. The factors maintaining circulatory equilibrium, cardiac output, blood volume, venous pressure, blood pressure and circulation time) are defined and discussed.

Historically the importance of cardiodynamic studies in explaining the nature of, and circulatory mechanisms involved in certain clinical conditions such as hypertension, central *vs.* peripheral failure, right *vs.* left heart failure, hyperthyroidism and polycythemia are stressed.

It has been found useful from the diagnostic and therapeutic points of view to group decompensated cardiacs into plus and minus forms of failure, based on blood volume readings.

From the practical viewpoint, the greatest uses made of cardiodynamic studies are in the following:

1. Borderline cases of hyperthyroidism, where an increased cardiac output, increased blood volume and rapid circulation time distinguish this condition from neurocirculatory asthenia or incipient tuberculosis (in which the above values are normal).

2. In polycythemia vera, the very high blood volume and hematocrit reading is usually sufficient to distinguish it from the symptomatic polycythemias, which do not yield such high figures.

3. In the differentiation between right and left heart failure, aside from clinical differences, the lengthened arm-to-lung circulation time in right-sided failure is of distinct value. By subtracting the arm-to-lung circulation time from the total pulmonary circulation time (arm-to-head) one can estimate the speed through the left heart circuit.

4. In decompensation, often the very first sign of right heart failure is an increase in the venous pressure.

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* Our results are in disagreement with Tarr, Oppenheimer and Sager,¹⁵ who found a moderate to marked prolongation of circulation time in polycythemia.

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MOVEMENTS OF ROENTGEN-OPAQUE DEPOSITS IN HEART VALVE AREAS.

II. THE EXCURSION OF THE APEX AND BASE OF THE LEFT VENTRICLE COMPARED WITH THAT OF THE LEFT BORDER.

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IN 1937 we published a study based upon roentgenkymograms of Roentgen-opaque deposits in heart valve areas.^{3b} At that time our material consisted of 3 cases, in 1 of which there was calcification of the mitral valve (proved by necropsy) and in the other 2, involvement of the aortic valve area. The technique used and the important limitations of the method were described. In all 3 cases there was an extensive movement of the Roentgen-opaque masses toward the apex during systole. It had been pointed out by Dietlen¹ as long ago as 1910 that during systole the cardiac apex moves upward and inward toward the base. We had frequently observed this phenomenon in patients in whom the apex was visible above the diaphragm and had made several roentgenkymograms of the apical movement. Unfortunately, however, none of the 3 patients with calcified valves could be placed in positions in which the apex was visible above the diaphragm (probably because of the fact that all had cardiac enlargement). We were unable therefore to make roentgenkymograms of the apex for comparison with the movement of the calcified areas. Nevertheless, we regarded the evidence at hand as adequate to support the conclusion that the important feature of left ventricular contraction is shortening of the long axis and that furthermore, not only does the apex move toward the base, but the base moves toward the apex. Compared with the

movement of Roentgen-opaque masses in the 2 cases in which kymograms of the left border were also made, it appeared that the movement of the left border was of much less extent than that of the apex and base. The effect on auricular filling of this unexpectedly great movement of the base during ventricular systole was also discussed.

In the last 18 months we have studied 2 more cases with Roentgen-opaque masses in the region of the aortic valve, dense enough to show satisfactorily in roentgenkymograms. In 1 of these the findings were practically identical with those of Cases 2 and 3 of our former paper and therefore need not be presented. The other case was unusual in that, despite the presence of a fairly dense calcium deposit in the region of the aortic valve (Fig. 1), the heart was not enlarged, and there were no clinical signs of aortic valve disease. This suggested that the calcium did not involve the leaflets to any great extent and was probably in the neighborhood of their attachments. The cardiac apex could be separated from the diaphragm by having the patient take a deep breath.

A roentgenkymogram was made with the patient placed in such a position of recumbency that movement of the apex and the calcium deposit toward and away from each other could be seen through the horizontal slit of the roentgenkymograph with the Roentgen ray beam centered halfway between the calcium mass and the apex. It was possible in this manner to include movement of both the calcium deposit and the apex in one exposure. The kymogram was made according to the technique we have described previously,^{3a} and was timed by a simultaneously recorded electrocardiogram. A roentgenkymogram timed by an electrocardiogram was also made of the left ventricular border.

The results of the studies are shown in Figures 2 and 3. It may be seen that very early in systole, the calcium deposit begins to move abruptly toward the apex as it did in the other 4 cases. At almost the same instant, movement of the apex toward the base begins. Both of these movements continue during systole; the excursions are comparatively wide. In Figure 3, the much smaller excursion of the left ventricular border is seen. In early ventricular systole when the apex and base are moving rapidly toward each other, the left ventricular border is actually moving outward instead of inward.* It does not recover the ground lost until nearly the middle of systole, but the slow inward movement begins after the initial outward movement and continues during the remainder of systole.

* Outward movement of the left border is the rule during the early part of ventricular systole. This movement, although due to ventricular contraction, is a resultant of changes in shape and size of the ventricles and movements of the heart as a whole, such as rotation. The complexity of the movements makes attempts to evaluate the importance of each factor uncertain in result. At any instant, they may tend to move the border in the same direction or in opposite directions.



FIG. 1.—Roentgenogram of the patient in the left oblique position. This view was selected because it best demonstrates the extent of the calcium deposit (indicated by arrows). The separation of the heart from the diaphragm is not seen with the patient in this position. During exposure the print was subjected to "dodging" to improve contrast in the region of the valves.

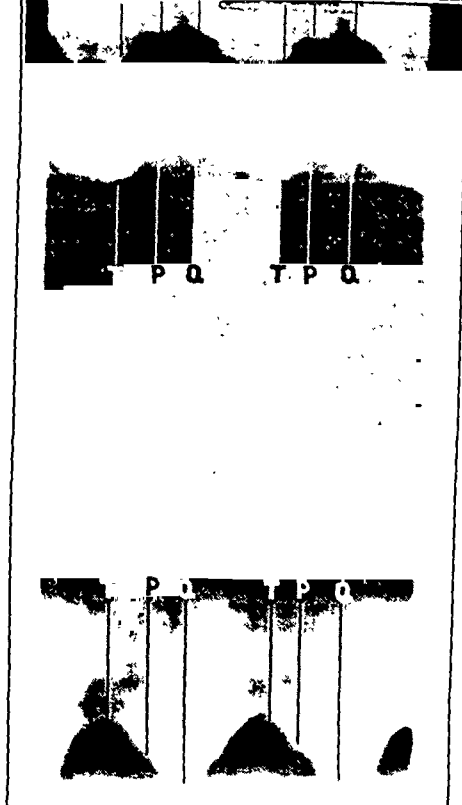


FIG. 2.—Roentgenkymogram with the patient in the dorsal recumbent position with right side facing the horizontal slit. Movements of the calcium deposit in the aortic area and of the apex toward each other during systole and away from each other during diastole. The calcium deposit is shown at the top of the print and the apex at the bottom (impinging slightly on the diaphragm at the end of diastole). The sequence is from left to right. *T* corresponds to the end of the *T* wave of the electrocardiogram and *P* and *Q* to the beginning of the *P* and *T* waves respectively. During exposure, the print was subjected to "dodging" to improve contrast. The size of the print has been reduced 33% in reproduction.

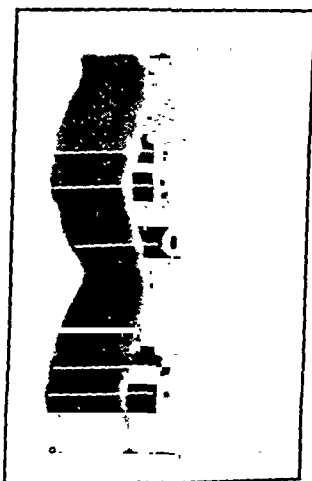


FIG. 3.—Roentgenkymogram of the left ventricular border made with the patient in the antero-posterior position in order to record lateral movement. The level was nearer the apex than the base, approximately 2 cm. above the diaphragm. *T*, *P* and *Q* refer to the same electrocardiographic events as in Figure 2. The sequence is from top to bottom. The size of the print has not been altered in reproduction.

Recently we have made fluoroscopic studies of a patient in whom the part of the right coronary artery lying in the auriculo-ventricular groove was seen to be calcified. During ventricular contraction this part of the artery and the apex moved toward each other. We regarded this as evidence that the auriculo-ventricular groove was being pulled toward the apex.

Discussion. In addition to the limitations of the method and the precautions that must be observed in the interpretation of results which were discussed in our former paper, there are still other factors to be considered in studies such as that shown in Figure 2. The centering of the Roentgen ray beam halfway between the calcium deposit and the apex, and the spatial relations of these areas to the position of the target and film, influence, to at least a slight extent, the magnitude of the recorded movements. The two chief factors, however (divergence of rays and lack of parallelism between the slit and the long axis of the heart), tend to counterbalance each other. A calculation of the maximum possible error which could occur from these sources indicates that it is small, and can be disregarded in the present discussion.

The conclusion reached in our former paper that the important movement of the left ventricle during contraction is shortening of the long axis with extensive movement of the base and apex toward each other is confirmed by the findings in this case. Likewise, it is shown that the movement of the left border is a relatively small part of the cardiac movement and that, as a matter of fact, this part of the heart border may be moving outward during at least part of the period of contraction. It would therefore seem justifiable to conclude that roentgenkymography of the left ventricular border may fail to reflect the most important part of movement during contraction.

The fact that in each of the 5 cases we have studied there has been an extensive movement of the calcified tissues toward the apex (the present case showing less than any of the others) tends to confirm the view previously expressed regarding auricular filling. The floor of the auricles must be pulled downward during ventricular contraction, along with the calcium-bearing tissues at the base of the ventricles. This movement would tend to fill the auricles by forcible suction. We have no means of estimating with any accuracy the part this process plays in auricular filling but it seems to be an important factor. The marked emptying of the cervical veins which occurs during ventricular systole (easily demonstrated by optically recorded phlebograms timed by some cardiac activity such as is represented by the electrocardiogram) suggests that the floor of the right auricle is also pulled downward during ventricular systole.* In addition to the forcible filling of the auricles that must occur

* This explanation for the sharply descending wave in the jugular phlebogram during ventricular systole is not new. It has been discussed by Wiggers.²

during ventricular systole, the relaxation of the ventricles during diastole and the upward movement demonstrated in the calcium-bearing tissues, suggests that this process under certain circumstances may also aid in ventricular filling.*

One effect of forcible systolic pull of the root of the aorta toward the apex is that the blood does not have to be propelled quite so far during systole to enter the aorta as it would if the aortic valve were fixed in position. Roentgenkymograms of the ascending aorta occasionally show an inward movement of the aortic wall just before the outward thrust of the pulse. A similar phenomenon is occasionally observed in carotid pulse tracings. It now seems probable that this preliminary wave is due to downward pull on the root of the aorta beginning during the isometric contraction phase. The major part of the downward pull, however, occurs during ejection. To what extent it may alter the contour of the pulse wave is not certain. It is probable nevertheless, that one of its effects is to lessen the impact of the blood on the aortic wall.

Summary. A cardiac roentgenkymogram timed by an electrocardiogram was made in such a way as to demonstrate the movements, toward and away from each other, of the apex and of a calcium deposit in the region of the aortic valve. From the data obtained in this case and 4 others (3 previously published) in which roentgenkymograms were made of calcium deposits in either the mitral valve or aortic valve area, the following points are emphasized.

1. The change in size and shape of the left ventricle during contraction is probably due more to shortening of the long axis than to movement of the lateral wall.

2. The floor of the auricle (roof of the ventricle) does not remain in a relatively fixed position as is usually assumed, but is pulled vigorously toward the apex during ventricular systole, while the apex is moving toward the base. The directions of movement are reversed in diastole.

3. The movements of the left ventricular border are much smaller than the movements of base and apex. The shortening of the long axis may be so great that the left border actually moves outward during the early part of systole. The foregoing facts should be taken into consideration in any attempt to study ventricular contraction by means of recording the movements of the left ventricular wall. These movements may fail to reflect the vigor or extent of the left ventricular contraction.

* It would be difficult to understand how hearts almost completely encased in calcium and therefore capable of little or no external movement could continue to function otherwise. The vigorous downward pulling of the tissues between the auricles and ventricles during systole (helping to fill the auricles and empty the ventricles) and upward movement during diastole (helping to empty the auricles and fill the ventricles) is probably an essential part of the mechanism which permits the patient to survive until the external walls of the heart are relieved of some of their restriction by operation.

4. The marked movement of the auricular floor, as a result of ventricular contraction, must create a powerful suction which is an important factor in bringing about auricular filling.

5. It is probable that when movements of the external walls of the heart are restricted, the filling and emptying of its chambers are made possible by the effects of ventricular contraction and relaxation on movement of the tissues separating auricles and ventricles.

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HISTOLOGIC INVESTIGATION INTO THE PYLORIC GLAND ORGAN IN PERNICIOUS ANEMIA.*

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THE present histologic investigations into the pyloric gland organ in pernicious anemia in man form a continuation of earlier work by Meulengracht *et al.*^{16a-f.17.18} carried out in this Clinic on the localization of the anti-anemic factor ("intrinsic factor") demonstrated by Castle in the stomach.

We learn from this earlier work that the pig's stomach, both histologically and functionally, is divided into two distinct parts: a fundus portion, containing fundus glands with parietal and chief cells secreting hydrochloric acid and pepsin (rennin), and a pyloric portion, containing pyloric glands with the large clear pyloric gland cells secreting the anti-anemic factor. We further learn that an anti-anemic activity, demonstrated in the duodenum, must be attributed to Brunner's glands, which, histologically, are identical with the pyloric glands, so that both sets of glands must—at least in this respect—be regarded as constituting a functional entity, and it was suggested to give them the common name, *pyloric gland organ*.

As the investigations showed that it is the pyloric gland organ which produces the anti-anemic factor of the stomach, one might reasonably assume that this organ becomes atrophic or for some other reason does not function in pernicious anemia; it was therefore decided to undertake a histologic examination of the pyloric gland organ in patients with pernicious anemia.

Earlier Investigations. There exist numerous investigations into the histology of the stomach and, to some extent, of the intestine,

* This work was carried out with the support of P. Carl Petersen's Fund.

in pernicious anemia. They were started as far back as 1870 by Fenwick,⁷ who demonstrated atrophy of the gastric mucous membrane. Since then, as mentioned, numerous investigations have been undertaken. Those of Faber and Bloch,^{6a,b} Lange,¹⁴ and Wallgren²⁴ may be regarded as the most important, because the material used was fixed according to Faber and Bloch's method^{6a,b} by means of intraabdominal formaldehyde injections immediately after death. The material is thus protected against postmortem changes which damage the histologic picture. The numerous histologic investigations show that the stomach itself is always the seat of a severe gastritis with interstitial changes in pernicious anemia, most pronounced in the fundus portion where there is atrophy of the glands and destruction of the specific glandular elements, namely, the parietal and chief cells. The changes seem to be less striking in the pyloric portion, but more detailed information of this region is not available. Our knowledge of the condition of Brunner's glands is extremely scanty. In the histologic descriptions of the individual cases in the works of Faber and Bloch,^{6a,b} as well as those of Lange,¹⁴ remarks may be found, such as: that the interstitial changes in Brunner's glands are small, or that Brunner's glands seem relatively well preserved, or that Brunner's glands appear normal, and so on, but more detailed information is not given. One gets the impression that attention has not been especially directed to this point.

At the International Hæmatological Congress in Münster, held in 1937, I^{16f} communicated the first results of my histologic investigations into the pyloric organ in patients with pernicious anemia, from which it appeared that the pyloric and Brunner's glands seemed surprisingly well preserved, an observation which was confirmed in 1938 by Magnus and Ungley.¹⁵

Author's Investigations. Material. During the last few years I have collected 9 stomachs with the corresponding duodenums from patients diagnosed as cases of pernicious anemia. These patients had died either from pernicious anemia, having been admitted to hospital *in extremis*, or from intercurrent diseases, their anemia being more or less compensated.

In 8 of the cases, the diagnosis was confirmed by the characteristic course of the disease, with a typical blood picture, gastric achylia and by subsequent response to specific therapy. The clinical diagnosis was very doubtful in 1 case, and the postmortem findings made the diagnosis still more doubtful; in fact, the subsequent histologic investigation of the stomach places this case in a class by itself.

Technique. The organs of all the 9 cases examined were fixed immediately after death by the method of intraabdominal injection of formaldehyde, devised by Faber and Bloch.^{6a,b} Different concentrations and amounts can be used, but my impression is that the best material is obtained by using a greater amount of a little weaker solution. The following scheme

was adopted: 600 cc. of 5% formaldehyde solution were injected in 5 different situations, where the stomach and duodenum were thought to be. The aim was to inject some of the fluid into the stomach, and in some cases excellent fixation was obtained, to the exclusion of postmortem changes of a digestive or other nature, but in other cases the result was not very good, probably largely because the fluid did not enter the stomach. Still larger amounts of fluid ought perhaps to be used. The organs were removed after death and kept in the fixing fluid.

For the histologic investigations the stomach and duodenum were opened along the greater curvature and a series of sections were cut along the greater curvature and duodenum as far as the jejunum.

The material was prepared in the manner of "collared beef," that is to say, strips were cut out, longer or shorter according to their thickness, which were then rolled up like collared beef, tied together with thread, embedded, and when cut in this form each section contained a long piece of the stomach wall. In successful cases, one section will include 10 to 20 cm. or more of stomach wall.

Hematoxylin-eosin, hematoxylin-Congo red and Unna's polychrome methylene blue were used for staining.

The preparations were subjected to a qualitative investigation, but so far it has not been possible to examine them quantitatively.

The Normal Stomach. I feel justified in placing the Danish investigations, especially those of Bloch,² Lange,¹⁴ and Vimtrup²³ before other studies, because they were done on well-fixed material and because they made use of the stomachs of children and adults, where as far as possible it was ascertained beforehand that the subjects had normal stomachs. The best and most extensive investigations are attributable to Lange,¹⁴ in whose monograph the normal structure and amount of the various glands and interstitial tissue were investigated and described. They have to some extent been made accessible to a wider public by Faber.⁵

From these investigations, especially those of Lange,¹⁴ we have an accurate knowledge of the histology of the normal stomach. The descriptions agree with what I have been able to observe in my own normal material. Some of the chief points may be mentioned.

In the fundus of the normal stomach, the glands are closely packed together in palisade fashion. Above are found the gastric crypts covered with the surface epithelium; they occupy about one-fifth of the thickness of the mucous membrane. The fundus glands constitute the lower two-thirds, in the upper part of which the parietal cells with their eosinophil cytoplasm are especially prominent, while the chief cells with their basophil granular cytoplasm mainly occupy the basal part. The glands are placed so closely together in palisade fashion, as has been mentioned, that there is practically no interstitial tissue; only a very few connective tissue cells belonging to the tunica propria, and a very few round cells, chiefly lymphocytes, are found. In the pyloric portion the crypts are longer, the glands are of a slightly different structure, they are not quite so closely packed, and they tend to branch into

alveoli down toward the muscularis mucosæ. The type of cell here is the large clear pyloric cell, which lines the branching lumina of the gland down to the muscularis mucosæ. The interstitial tissue is still scanty, but more abundant than in the fundus. The cells are connective tissue cells belonging to the tunica propria, and a few round cells, mainly lymphocytes. A solitary flat lymphoid follicle is very rarely found just above the muscularis mucosæ in the fundus and in the pyloric portion.

The picture changes on the other side of the pylorus: the mucous membrane is now typical intestinal mucous membrane, with cuticular cells and goblet cells; and at the bottom of the Lieberkühn crypts, Paneth cells are seen. There is abundant interstitial tissue, with numerous round cells in the intestinal mucous membrane. Under the muscularis mucosæ, Brunner's glands are seen spreading out in the submucosa. They occur as closely packed gland lumina, lined with large clear cells of the same shape and appearance as the pyloric gland cells; the lumina lie so tightly packed together that there is practically no interstitial tissue. The cells seen are only an occasional tunica propria connective tissue cell and a very few round cells.

The various types of glands are distributed in the human stomach in the following manner: around the esophageal opening there is a narrow band, a few millimeters broad, of so-called "cardiac glands," which mostly resemble dislodged pyloric glands (compare the arrangement in the pig); next comes the large fundus portion, which only contains fundus glands. Then near the pylorus there is a smaller region which only contains pyloric glands. According to Buechner³ and Paschkis and Orator,¹⁹ they extend for about 6 cm. into the stomach from the pyloric ring along the lesser curvature. At the pylorus the pyloric glands commence to dip down under the muscularis mucosæ, and are then continued as Brunner's glands in the submucosa; they are largest and most compact just past the pyloric ring, but gradually diminish in size and numbers and disappear at about 10 to 20 cm. from the pylorus. They extend therefore a good distance beyond the ampulla of Vater.

The Stomach in Pernicious Anemia. On examination, the 8 stomachs from cases of pernicious anemia in which the diagnosis had been made absolutely certain by clinical investigation and autopsy findings, all showed, on the whole, similar changes.

The Fundus Region. *The Surface Epithelium and the Crypts.* In places where fixation was imperfect, it was often difficult to form a definite opinion of the condition of the surface epithelium; but where the fixation was successful it appeared to be well preserved, though frequently the cells were shorter, more cubical, than normal. Round cell infiltration was a little more marked than normal, but was not very pronounced.

The crypts were often considerably shorter than normal, and

they were more widely separated from one another by more abundant interstitial tissue.' This was especially the case when there was atrophy of the mucous membrane; and if the atrophy was pronounced the crypts largely disappeared, in fact they might be entirely deleted, so that the mucous membrane presented a smooth, even surface, covered by somewhat flattened surface epithelial cells.

In some situations the surface and crypt epithelium was replaced by typical intestinal epithelium, with cuticular and goblet cells, and at these points ducts of glands penetrated the mucosa down to the muscularis mucosæ, of the same form and appearance as the Lieberkühn crypts, with Paneth cells at the bottom. The portions covered by the intestinal type of epithelium took the form of islands, "intestinal islands." Metaplasia of the gastric mucosa into intestinal mucosa had occurred here. Intestinal islands, which are a well-known phenomenon in all forms of chronic gastritis, were found in 7 of the 8 stomachs.

The Fundus Glands. While, as mentioned above, the fundus glands are placed regularly close together in palisade fashion in the normal stomach, in the 8 stomachs examined they were separated from each other by a considerable amount of interstitial tissue, and their structure was entirely different so that they could no longer be recognized as fundus glands. They were, as a rule, irregularly tortuous and branching. Clusters of very small atypical gland lumina were often seen lying together. In other situations also or in other stomachs lumina could be seen which were more or less dilated into cysts. A cystic dilatation of the gland lumina was a very characteristic phenomenon in some of the stomachs ("cystic gastritis"). The glandular epithelium was entirely altered in character. The parietal cells had quite disappeared, nor could the chief cells with the basophil properties be recognized, at least not with any certainty. In place of these two specific types of epithelial cells, the gland lumina were lined with an undifferentiated epithelium, the cells of which varied greatly in shape and height, in the small lumina being a little higher and in the cystic dilated lumina often quite flat; the nuclei and cytoplasm presented no special characteristics.

The Interstitial Tissue. The interstitial tissue was, as stated, greatly increased in amount, because of the accumulation of closely packed cells. In comparison with the normal stomach, where the palisades of closely packed fundus glands barely leave room for a single cell in the interstitial tissue, this was strikingly the most obvious change. The increase only to a very small extent involved connective tissue. The characteristic feature was the broad compact belts of round cells, which insinuated themselves between the irregular, deformed gland lumina and up between the crypts. The main types of cells were lymphocytes and plasma cells. The lymphocytes were only sparsely distributed in the interstitial tissue.

the greater part of them being aggregated in lymphoid follicles. In some cases these were exceedingly numerous ("follicular gastritis"), while in other cases they were less abundant; but they were always a striking feature when compared with the histologic appearance of the normal stomach, where they are, as mentioned, scarce. They were always situated low down near the muscularis mucosæ, but from here they might extend up through practically the whole thickness of the mucosa. The interstitial tissue in their neighborhood contained a more liberal supply of lymphocytes. Otherwise, plasma cells were the predominant type in the interstitial tissue. They had the characteristic nuclei and the abundant strongly basophil cytoplasm, and lay in dense masses everywhere in the mucosa between the gland lumina. Neutrophils were very rare. Very frequently large cells were seen with small dense nuclei and abundant eosinophil and somewhat granular cytoplasm (Russell bodies). This type of cell is nearly always found in chronic gastritis, and is regarded as a phagocytic cell.

As a result of the aforesaid changes there was a definite atrophy of the whole mucous membrane in most of the cases. It was sometimes quite thin, with a smooth surface and scanty glandular elements. It must be recognized, however, that this appearance may have been partly an artefact. Thus parts of the stomach were observed which had been fixed in a greatly dilated condition, so that the whole wall was quite thin, and other parts which had been fixed while greatly contracted, the whole of the wall being quite thick. In the former situations a thin and smooth mucous membrane, apparently completely atrophied, was seen microscopically, while in the contracted portions the mucous membrane seemed to be heaped up, appeared thicker and did not give the same immediate impression of atrophy. An estimate of the thickness and atrophy of the mucous membrane must therefore be made with reserve, and with reference to the state of contraction; the best guide is the thickness and structure of the muscularis mucosæ in the particular preparation. On taking these points into consideration, I believe that in all the cases I have been able to ascertain that there was some degree of atrophy of the mucous membrane in the fundus.

The Pyloric Region. On passing from the fundus to the pylorus the gastritic changes in the 8 stomachs gradually diminished; they were still present, but less pronounced. This was the chief impression conveyed.

The Surface Epithelium and the Crypts. The surface epithelium appeared to be well preserved. It did not seem to be at all flattened. There was little or no change in the cells. Metaplasia to the intestinal type of epithelium was not observed. Here also the *crypts* were a little more separated from one another than in the normal stomach, because of the somewhat greater amount of interstitial

tissue, but this was not very marked. The length and appearance of the crypts seemed normal.

The Pyloric Glands. On account of the slight increase in interstitial tissue, the glands here also were more widely separated than normal, but otherwise their normal form and appearance was preserved. There was no distortion or process of repair, and no cystic enlargement; in the vicinity of the muscularis mucosæ where the glands form crypts, the apparently uniform gland lumina were found in the usual small groups of small lobuli. It is possible that in some of the cases they showed a slight reduction in number and extent, but I have not been able to demonstrate any great diminution. The different gland lumina were normal in appearance, and the cells exhibited the same abundant clear cytoplasm as normal ones, with the same finely reticular structure, and a round or oval nucleus usually situated toward the base. As in the normal stomach, the pyloric glands were most numerous in the vicinity of the pyloric ring.

The Interstitial Tissue. To ascertain whether or not this was pathologically increased was a little more difficult here than in the fundus, because there is normally more interstitial tissue with more cells in the pyloric portion than in the fundus, where, as mentioned, there is hardly any to be found. There is nevertheless no doubt that the interstitial gastritic changes in all the cases extended into the pyloric region; there was perhaps a small increase in the connective tissue, but here also it was especially the cells which were increased. Again the cells were mainly lymphocytes and plasma cells; the lymphocytes had the same tendency as in the fundus to collect in lymphoid follicles, which were abundant, or in dense belts which resembled follicles. The plasma cells were more scattered among the crypts and glands. In most of the cases there were occasional Russell bodies.

The Duodenum. When we come to the intestinal mucous membrane of the duodenum just past the pylorus, it is very difficult to be certain whether the inflammatory changes reached this point. The interstitial tissue of the intestinal mucosa is normally so rich in cells that it is difficult to recognize a small increase in the number or a slight alteration in the type of cell. A very thorough preliminary study of the normal mucous membrane of the duodenum is essential.

Mucosa. On examining the mucosa of the duodenum in the 8 cases of pernicious anemia nevertheless, one quickly realized, in spite of the above reservation, that no great change could have occurred. The coarser structure, with valvulæ Kerkringii and intestinal villi, was not markedly altered; the thickness of the mucous membrane appeared normal; the crypts of Lieberkühn seemed to be of normal structure and length, and were lined by cuticular cells and goblet cells and with Paneth cells at the base.

A superficial examination of the amount of interstitial tissue and type of cell did not show any demonstrable deviation from the normal.

Brunner's Glands. Interest is centered primarily on Brunner's glands, and the findings in the main were similar in all the 8 cases of pernicious anemia. Here also Brunner's glands made their appearance just beyond the pylorus, as in normal cases, and it was clear that it was the pyloric glands, which now began to dip down under the muscularis mucosæ, and spread out in the submucosa. In all the 8 affected stomachs they were found in the greatest numbers and the largest lobuli just below the pyloric ring, and for a distance of a few centimeters. In the present investigation, no attempt has been made to decide whether there has been any alteration in number and size, that is to say, any quantitative deviation, and all that can be said here perhaps is that at any rate the change was not striking. But this question will be taken up later in this discussion. With regard to the restricted qualitative investigation, the results in all the 8 stomachs were the same; histologically, no definite pathologic changes could be demonstrated.

The structure of the glands, with their closely packed uniform lumina forming lobuli of varying size in the submucosa, was normal. Each lumen was normal in appearance, small, and surrounded by a few tightly packed cells. With the staining method used, no histologic changes were seen in the actual cells; they were characterized by the usual abundant clear cytoplasm with the typical fine reticulate structure, and by the round or oval basal nuclei. Only in 1 case was I struck by the fact that the cells were flatter than normal, and the lumen thus a little larger. The cells were here less clear, the nuclei were found and were situated at the base, though more in the center of the cells. I do not know whether this is an altered functional condition or phase. Interstitially, there were only a few tunica propria cells between the closely packed gland lumina, and here and there an occasional plasma cell in the angles between the contiguous lumina, but this seems to be what is normally observed.

This was the picture seen in the 8 stomachs, but in the case of the ninth stomach (Case 9) there was some divergence from these findings.

This stomach also showed evidence of gastritis in the fundus, with considerable interstitial changes. The fundus glands were somewhat atypical and atrophied, but the atrophy was very much less pronounced, and there were a good number of apparently well-preserved parietal cells, which reached as a belt in the mucous membrane from the base of the crypts to a little distance above the muscularis mucosæ, where they were replaced by cells which resembled typical chief cells. In the pyloric portion there was slight gastritis, but an

apparently well-preserved gland system. Brunner's glands seemed quite normal.

The presence of fairly well-preserved parietal and chief cells was thus quite unusual.

A review of the clinical case sheet and the postmortem report, however, strongly suggested that it was not a case of true pernicious anemia (see case report).

If therefore we confine ourselves to a consideration of the findings in the 8 stomachs, where the diagnosis of pernicious anemia can be regarded as being definitely established both clinically and pathologically, we can summarize the results as follows:

All the cases exhibited severe gastritic changes in the fundus, with atrophy of the fundus glands, and disappearance of the specific glandular elements, that is, the parietal and chief cells. The gastritic changes continued down into the pyloric portion, but they were obviously less pronounced there, and the pyloric glands seemed relatively well preserved, as also did the gland cells both in number and appearance. Finally, it may be said of Brunner's glands that they appeared absolutely normal, at any rate qualitatively.

The histologic changes were thus most marked in the region of the hydrochloric acid-producing and pepsin-producing fundus glands, but less marked in the pyloric gland region, and entirely absent in the vicinity of Brunner's glands.

Discussion. The result of the investigations was thus rather surprising and different from what I had expected, because it seemed probable that the chronic gastritis with atrophy of the glands would extend down to the pyloric gland organ and compromise its action. But we must acknowledge that the changes are mainly connected with the hydrochloric acid and pepsin-producing portion of the stomach, while the pyloric gland organ was moderately intact.

The question is now whether this affects the earlier investigations, the result of which was that the anti-anemic factor is produced by the pyloric gland organ.

I do not think that this is the case. The therapeutic experiments with different fractions of pig's stomach, on which this result was based, undoubtedly carry great weight. They have, moreover, been confirmed in Holland (Groen¹⁰), in Denmark (Gram⁹), in England (Ungley²²) and in the U. S. A. (Thompson²¹). They are also supported by the broad experiment represented by the routine treatment of patients suffering from pernicious anemia with pylorus powder (pylorin), as it is carried out in Denmark. From material at this hospital, Alsted¹ has already shown that when using pylorus powder one-half the dose suffices, compared with the amount required when a powder of the whole stomach is employed. This has later been confirmed by very extensive daily experience.

One must therefore undoubtedly seek another explanation which

will bring the two series of investigation into harmony with one another.

It is thus possible, although my present impression is that it is *improbable*, that a *quantitative* examination of the pyloric gland organ in patients with pernicious anemia may disclose changes in the number and amount of the specific glandular elements.

It is expected that Danish histologic investigations will be available shortly which will establish a normal basis for comparison of the glandular elements in this region.

The possibility of a *functional insufficiency* should also be kept in mind in future investigations. The functional capacity of an organ cannot be determined from its anatomic condition alone. There is really nothing to prevent a pyloric gland organ, anatomically intact or only slightly affected, from having its function impaired for some other reason. In this connection it is worth while to bear in mind the conditions in diabetes. It has been established beyond doubt that the pancreas islands produce insulin and that its production is reduced in diabetes, and yet search as to whether or not there is atrophy of the pancreas islands in diabetes yielded conflicting results. It is also expedient to draw attention to Goldhamer's⁸ experiments which indicated that it was the *volume* of the gastric fluid which was reduced in pernicious anemia, while the anti-anemic activity per unit volume was the same as under normal conditions. The gastric fluid was obtained by continuous suction, and it was found that, while the amount of secretion in normal persons averaged 150 cc. per hour, the mean volume was 20 cc. per hour in patients suffering from pernicious anemia. It was found that there was a relation between the amount of gastric juice and the number of red blood corpuscles, and when the gastric juice was subjected to Castle's test, that is, incubation with muscle meat and administration of the mixture to patients with pernicious anemia, the anti-anemic activity per unit volume was preserved. These experiments require confirmation, but they render it very possible that a functional insufficiency may be present. We do not know the way in which the function of the pyloric gland organ is regulated or whether there may be a hormonal "pacemaker" for the secretion. We know that such a process occurs in the case of the pancreatic juice, where the secretin of the duodenal wall starts and maintains the pancreatic secretion after the manner of a hormone. It is therefore not very improbable that a similar mechanism may obtain in the case of the pyloric gland organ and that here also there might be a substance which influences the secretion like a hormone does, and which might, for instance, under normal conditions be a product of the stomach wall (? fundus portion) and might be absent or diminished in amount in pernicious anemia.

Finally, we must consider the possibility that *processes in the intestine* are wholly or in part responsible. Castle's hypothesis, which is still generally accepted, includes three factors: 1, A sub-

stance which is secreted by the stomach glands, namely, the gastric factor or Castle's "intrinsic factor"; 2, a substance obtained from the food, the food factor or Castle's "extrinsic factor"; and, 3, a completed substance, elaborated from these two bodies, the liver factor.

The completed substance, the liver factor, is thus produced by interaction between the two first factors. This action probably must be ascribed to the intestine, especially the small intestine. From numerous observations on the occurrence of pernicious anemia in association with diseases of the small intestine—tapeworm, multiple strictures of the small intestine, sprue—we know that the small intestine, in some way or another, must play a part in the processes which control the normal formation and absorption of the completed principle. In his latest published work (1937), Castle *et al.* maintains, on the basis of many varying incubation tests, that the essential part of the interaction between the intrinsic factor and the extrinsic factor occurs in the small intestine. It is clear that the question of the most suitable medium for the completion of these processes in the intestine, pH and other factors, thus becomes paramount; and even with a relatively well-preserved pyloric gland organ, in fact even when its function is comparatively intact, it seems possible that the achylia under certain conditions might change the milieu of the small intestine in a direction unsuitable to the course of the processes concerned.

This is hardly the place for a detailed discussion of these different possibilities, I only wish to draw attention to some of the problems for future investigation. I believe that two facts have been established: 1, That the anti-anemic factor of the stomach is produced by the pyloric gland organ; but, 2, that a histologic investigation shows that the pyloric gland organ is relatively intact in pernicious anemia. Perhaps the latter discovery renders the problem still more complicated, but, as an English colleague expressed it during a visit, "it makes it all the more fascinating."

Case Reports. CASE 1.—K. M. H. A., aged 40, died Sept. 21, 1933.

Clinical diagnosis: Pernicious anemia partly compensated, myelopathy, right pneumonia, right pulmonary abscess, *B. coli* pyuria.

Postmortem findings: (Dept. B, No. 144) Pernicious anemia, right pneumonia, right pulmonary abscess, right pleurisy, pulmonary edema, cirrhosis of the liver, perisplenitis, left parovarian cysts.

The bone marrow of the femur was red, megaloblastic erythropoiesis was seen microscopically.

Histologic examination: The fundus exhibited severe gastritis with disappearance of the specific glandular elements, chief cells and parietal cells. The gastritis gradually decreased down to the pyloric portion, but the pyloric glands seemed relatively well preserved. Brunner's glands appeared normal.

CASE 2.—M. M. P., a woman, aged 68, admitted Nov. 22, died Dec. 23, 1933.

Clinical diagnosis: Pernicious anemia.

Postmortem findings: (Dept. B, No. 186) Anemia of the organs, pul-

monary edema, chronic bronchitis, disseminated and confluent purulent bronchopneumonia, fibroid pleurisy, hydrothorax, steatosis cordis.

The bone marrow of the femur was red; megaloblastic erythropoiesis was seen microscopically.

Histologic examination: The fundus exhibited severe gastritis with pronounced interstitial changes and atypical glands with disappearance of the chief and parietal cells. The interstitial changes were less pronounced in the pyloric portion, and the pyloric glands appeared well preserved. Brunner's glands seemed normal.

CASE 3.—A. F. O., a woman, aged 69, admitted Oct. 24, died Nov. 9, 1934.

Clinical diagnosis: Pernicious anemia, myelopathy, cystopyelonephritis.

Postmortem findings: (Dept. B, 153/34) Pernicious anemia, cystopyelonephritis with calculus, acute infectious hyperplasia of the spleen, disseminated bronchopneumonia, arteriosclerosis.

The bone marrow was not described.

Histologic examination: There were pronounced interstitial and glandular changes in the fundus with disappearance of the chief and parietal cells, but only very slight interstitial changes in the pyloric portion with well-preserved glands. Brunner's glands were normal.

CASE 4.—B. K. P., a woman, aged 71, admitted Jan. 12, died Feb. 5, 1935.

Clinical diagnosis: Pernicious anemia, cystopyelitis.

Postmortem findings: (Dept. B, No. 16 d) Anemia of the organs, arteriosclerosis of the coronary arteries, pulmonary edema, chronic adhesive pleurisy, gall stones.

The bone marrow was not described.

Histologic examination: The entire fundus exhibited severe gastritis with profound changes in the glands and disappearance of the parietal and chief cells. The gastric changes continued down into the pyloric portion, although with a diminishing tendency, and the pyloric glands seemed relatively well preserved. There was perhaps a slight indication of interstitial changes in Brunner's glands which otherwise appeared normal.

CASE 5.—E. J. L., a woman, aged 77, admitted April 18, died April 24, 1935.

Clinical diagnosis: Pernicious anemia, cystopyelitis.

Postmortem findings: (Dept. B, No. 70) Anemia of the organs, slight jaundice, right bronchopneumonia, myocardial degeneration, subendocardial hemorrhages, subendothelial hemorrhages of the renal pelvis, fibrinopurulent cystitis, granular atrophy of the kidney.

The bone marrow of the femur was red.

Histologic examination: There were severe gastric changes in the fundus with disappearance of the chief and parietal cells. Moderate gastric changes occurred in the pyloric region with well-preserved pyloric glands. Brunner's glands were normal.

CASE 6.—L. J. J. J., a woman, aged 64, admitted June 24, died July 4, 1935.

Clinical diagnosis: Pernicious anemia partly compensated, cancer of the stomach, B. coli pyuria, arterial hypertension, cerebral thrombosis.

Postmortem findings: (Dept. B, No. 119) Senile atrophy, anemia of the organs, gastric cirrhosis, bilateral basal bronchopneumonia, aneurysm of the left ventricle of the heart, fibrosis of the myocardium, arteriosclerosis of the coronary arteries, cirrhosis of the liver, cholelithiasis of the gall bladder.

The bone marrow of the femur was not quite so red as in fresh cases of pernicious anemia. In places, it was a little gelatinous. A scirrhous cancer, not circular, was seen in the pyloric region. It extended as far as the pyloric ring.

Histologic examination: There were severe gastritis and atrophic changes in the fundus with disappearance of the chief and parietal cells. A carcinoma was present in the pyloric region, but the part around it exhibited

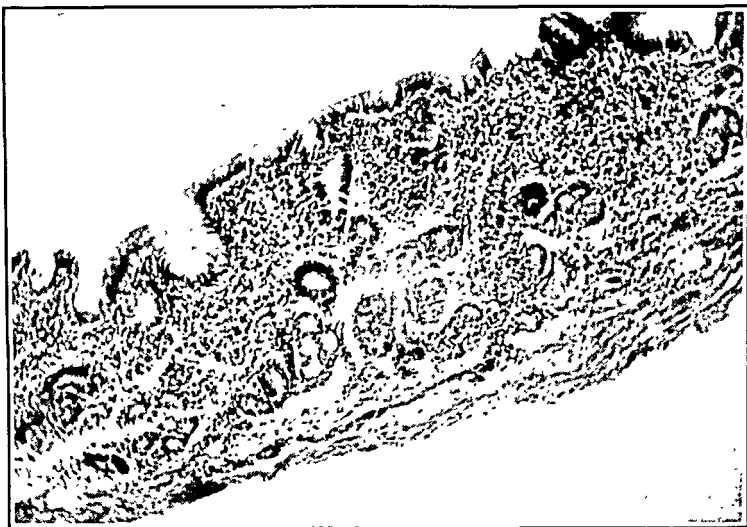


FIG. 1.—Case 7. Fundus mucous membrane. Interstitial gastritis, atrophy, deformity of glands, disappearance of chief cells and parietal cells.



FIG. 2.—Case 6. Fundus mucous membrane. Interstitial gastritis, atrophy, deformity of glands, disappearance of chief cells and parietal cells.



FIG. 3.—Case 2. Pylorus mucous membrane. Slight interstitial gastritis. Pylorus glands well preserved.

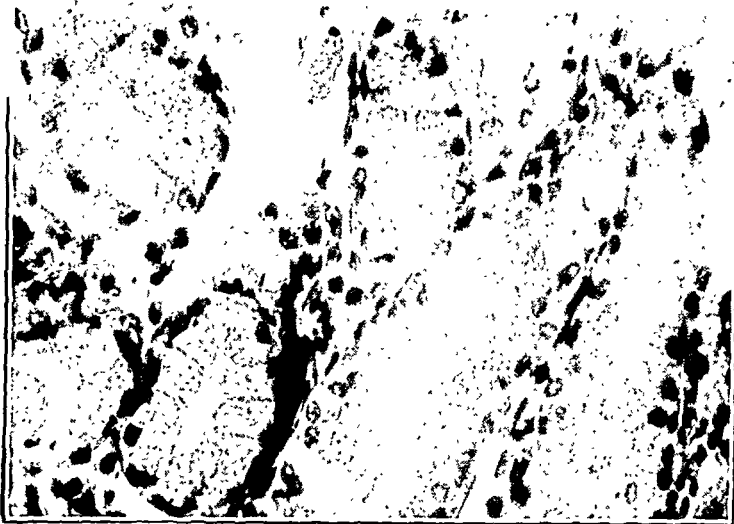


FIG. 4.—Case 2. Pylorus mucous membrane. Slight interstitial gastritis. Pylorus glands well preserved.



FIG. 5.—Case 2. Brunner's glands. No interstitial changes. Glands well preserved



FIG. 6.—Case 2. Brunner's glands. No interstitial changes. Glands well preserved.

only slight gastritic changes in the mucosa, and well-preserved pyloric glands. Brunner's glands appeared normal.

CASE 7.—L. V. C., a woman, aged 54, admitted Aug. 16, died Aug. 19, 1935.

Clinical diagnosis: Pernicious anemia, chronic progressive polyarthritis.

Postmortem findings: (Dept. B, No. 144 d) Anemia of the organs, parenchymatous degeneration of the liver, chronic valvular endocarditis of the mitral and chord, warty endocarditis of the mitral valve, atherosclerosis of the aorta, old infarcts of the kidneys, fibroid pericarditis, ecchymoses of the myocardium, pulmonary edema.

The bone marrow of the femur was red.

Histologic examination: There were severe gastritic changes in the fundus region with atypical glands and disappearance of the parietal and chief cells, and slight changes in the pyloric region, but the glands appeared well preserved. Brunner's glands seemed normal.

CASE 8.—L. S., a man, aged 68, admitted Nov. 25, 1935, died Jan. 11, 1936.

Clinical diagnosis: Pernicious anemia partly compensated, carcinoma of the stomach.

Postmortem findings: (Dept. B, No. 4 d) Anemia of the organs, carcinoma of the stomach, bilateral confluent and disseminated bronchopneumonia, bilateral chronic fibroid adhesive pleurisy, left interstitial chronic fibroid pneumonia, aneurysm of left ventricle of heart, old infarct of myocardium, atherosclerosis of the kidneys, hypertrophy of the prostate, vesical calculus, chronic cystitis, vesica trabecularis.

The bone marrow was not described.

An ulcerated carcinoma, about 8 by 7 cm. in size, was found in the pyloric region, some distance above the pyloric ring. It was not circular.

Histologic examination: The entire fundus exhibited severe gastritic changes with altered gland structure and disappearance of the chief and parietal cells. A carcinoma was present in the pyloric region. The interstitial changes were continued down into the pyloric region. They were rather pronounced in the vicinity of the cancer, but diminished as the pylorus was approached. No definite pathologic changes could be demonstrated in Brunner's glands.

CASE 9.—A. O. P., a woman, aged 72, admitted Aug. 16, died Aug. 17, 1935.

Clinical diagnosis: Severe anemia (pernicious?).

Clinical findings: The patient was in a desperate condition when admitted and died within 24 hours. It was found that 3 years previously she was in the General Hospital for anemia. The findings then were: Ewald's test meal, $\frac{3}{4}$ hour, 60 + 42 cc. 0/16; R.B.C.: 3,800,000; neutrophils: 28%; eosinophils: 6%; basophils: 1%; monocytes: 24%; lymphocytes: 41%. She had high fever now, was unconscious, extremely anemic and subicteric. The tongue was not quite smooth and free from papillæ. Hb.: 30%; R.B.C.: 1,265,000; color index: 1.2; white cells: 11,500; platelets: 255,000; Ewald's test meal was omitted this time.

Postmortem findings: (Dept. B, No. 142 d) Anemia of the organs, senile atrophy of the organs, right disseminated bronchopneumonia, left pulmonary infarct, left chronic fibroid and adhesive pleurisy, old apical pulmonary tuberculosis, myocardial degeneration, chronic fibroid cholecystitis, calculus of the gall bladder.

In the postmortem notes the bone marrow was described as follows: "*The bone marrow of the right femur was yellow, fatty.*" Macroscopically, the liver was normal, but microscopic necrosis was demonstrated around the ventral veins, some of them being infiltrated with neutrophils. The spleen was normal macroscopically, but a considerable number of "monocytoid cells" were seen in the sinuses microscopically.

Histologic examination: The fundus exhibited severe gastritis, but the glands were relatively well preserved with distinct parietal and chief cells. The gastritic changes were less pronounced in the pyloric region and the glands seemed well preserved. Brunner's glands appeared normal.

Summary. 1. It has been shown in earlier investigations that the anti-anemic factor in the stomach (Castle's intrinsic factor) is not found in the pepsin and hydrochloric acid-producing fundus portion, but in the pyloric portion and duodenum, and that it must be secreted by the pyloric glands and the histologically identical Brunner's glands.

2. The object of the present investigation was a histologic investigation of stomach and duodenum from 8 pernicious anemia patients, with special regard to the pyloric and Brunner's glands.

3. Gastritic changes in the fundus portion with atrophy of the glands and disappearance of parietal and chief cells were found in all the 8 cases. But the gastritic changes were less pronounced in the pyloric portion, and the glands seemed relatively well preserved; no histologic changes could be demonstrated in Brunner's glands.

4. How the above finding, which at first sight is rather surprising, can be brought into line with the present conception of the pathogenesis of pernicious anemia is discussed.

* The assistance of Dr. B. Vimtrup, Director of The Pathological Department, Bispebjerg Hospital, Copenhagen, and of Dr. Tage Strunge has been of great value to me as to the provision of normal anatomic material. In microphotographing, I have been further assisted by Dr. O. Arndal, Glendale, Calif.

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A CASE OF ERYTHREMIA, GOUT AND SUBLEUKEMIC MYELOSIS.

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THE relation between erythremia and leukemia, the complication of both diseases by gout and the rarity of gout in females justify a report of the occurrence, during a 5-year period, of all three conditions in 1 patient.

Case Report. E. R. (Surg. 42376, Med. 42089), at present aged 52, white, widowed, English-born housewife, entered the hospital November 17, 1932, complaining of a left abdominal mass of 6 months' duration. The family history was not contributory; there was no history of anemia, splenomegaly or gout. The past history was uneventful. Six months before admission the patient had first noted a firm, painless mass in the left abdomen, which increased in size causing tightness of the clothing. At this time menstruation ceased except for a scant 1 day flow 3 months later. For 6 months there was increasing constipation and 2 weeks before admission, slight nocturia. There was no significant weight change in the present illness.

Physical examination revealed a well-developed, fairly well-nourished, white female, mentally clear. The skin was somewhat florid. The lips, nail beds, conjunctivæ, buccal and nasal mucosæ, fingers and toes were bluish-red in color. Multiple small cutaneous telangiectases were present on the cheeks. The retinæ were deeper colored than usual, with engorged vessels. There were no retinal hemorrhages. The optic disks were normal. The lungs and heart were not remarkable. The blood pressure was 114 mm. mercury systolic and 74 mm. diastolic. The left abdomen was filled by a firm, smooth, non-tender, medially notched mass, presumably the spleen, extending slightly to the right of the midline, 17.5 cm. inferior to the xiphoid tip and 12 cm. below the left costal margin in the midclavicular line. By cystoscopic and pyelogram examinations the mass appeared to be the spleen, displacing the left kidney slightly medially. A smooth, firm, non-tender liver edge was palpated 2 cm. below the xiphoid tip. There was no lymphadenopathy. The superficial veins of the left leg were thrombosed. Roentgen-ray examination of the extremities showed no bone or joint abnormalities. The fingers and toes were not clubbed. Pelvic, rectal and neurologic examinations were normal.

Laboratory Studies. The urine sediment was normal, and the specific gravity ranged to 1.024. The phenolsulphonephthalein test gave an excretion of 90% in 2 hours and 10 minutes in 200 cc. of urine. The stool examination was negative. Gastric analysis, using the Ewald test meal, showed no free hydrochloric acid and total acidity ranging to .7 degrees of 0.1 normal sodium hydroxide in fractional specimens. The basal metabolic rate was +12% (DuBois standards). The vital capacity was 2.8 liters.

The Wassermann and Hinton blood reactions were negative. Carbon dioxide combining power (Van Slyke) was 53.8 vol. %. Blood urea nitrogen was 11 mg. %. Clotting time by the 6-tube method was 7 minutes (normal range 8 to 12 minutes); bleeding time (Duke's method) 2½ minutes; clot retraction normal. The blood platelet count was 600,000 per c.mm.

(normal). The hematocrit showed 50.6% cells, and individual cell volume 6.6 times 10^{-11} cc. A second determination (December 9) revealed 45.8% cells, and individual cell volume 6.8 times 10^{-11} cc. Icterus index was 9. Fragility test: patient's cells showed initial hemolysis in 0.46% NaCl, complete in 0.32% (normal controls showed initial hemolysis in 0.44%, complete in 0.34%).

Table 1 shows studies of the blood counts and smears.

TABLE 1.—BLOOD COUNTS AND BLOOD SMEARS IN A CASE OF ERYTHREMIA AND SUBLEUKEMIC MYELOSIS.

Date.	Hemoglobin, % (Sahli).	Erythrocytes, mil- lions per c.mm.	Leukocytes, thous- ands per c.mm.	Neutrophils, %.	Lymphocytes, %.	Monocytes, %.	Eosinophils, %.	Basophils, %.	Immature leukocytes, %.	Erythrocytes.
1932. Nov. 17	105	7.08	11.1	77	17	2	0	1	Unclassified, 3	Anisocytosis, poikilocytosis, occasional microcytes, occasional normoblasts; reticulocytes, 1.2%.
19	117	7.60								
20	16.15*	7.48	12.0	79	15	2	2	0		
21	..	7.39	12.3	81	11	3	2	0		
22	..	7.56	12.7	88	6	1	1	3		
26	16.04*	7.25	13.2							
28	105	7.66	18.5	86	6	1	3	3	Myelocytes, 2	Reticulocytes, 2.7%.
29	106	6.91	8.2							
30	82	11	1	5	1	...	Moderate achromia and anisocytosis.
Dec. 4	95	5.89	10.4							
9	116†	6.73	5.8							
10	102	6.24								
16	98	5.73	3.0							
17	3.1	72	22	1	4	1	...	As above; slight polychromatophilia.
1938. Jan. 15	60‡	3.60	7.5	76	18	2	2	2	Numerous band forms; myelocytes, 2	As above.
Apr. 2	70	3.70	7.2	76	15	4	3	2	Band forms, 30	As above; occasional tailed forms.
6	70	3.80	5.8	78	16	4	2	0	Myeloblast, 1	Reticulocytes, 0.9%.
14	60	3.60	6.8	As above.
18	70	3.65	4.9	76	12	6	0	0	Myelocytes, 6	As above; 1 nucleated red cell seen.

* Grams of hemoglobin per 100 cc. whole blood.

† Venous blood.

‡ Tallqvist method.

Clinical Course. On November 28, 1932, the patient was transferred from the surgical to the medical service for study and further treatment. On December 3, administration of Fowler's solution was started, 3 minims t.i.d., increasing 1 minim t.i.d., until the patient received 9 minims t.i.d. On December 12, puffiness of the eyelids, coryza, lacrimation, frontal headache, nausea and vomiting appeared, and medication was stopped for 1 day, then resumed at 6 minims t.i.d. with prompt disappearance of the above symptoms. The course was afebrile. The patient was discharged December 17, 1932, with the diagnosis of erythremia (polycythemia vera). During hospitalization the hemoglobin decreased from 105 to 98% (Sahli); the erythrocytes from 7,660,000 to 5,730,000 per c.mm.; the leukocytes to 3100; the constipation, nocturia and florid complexion disappeared, and the patient was less conscious of her abdominal mass, although the latter had not appreciably changed in size or consistency. Fowler's solution,

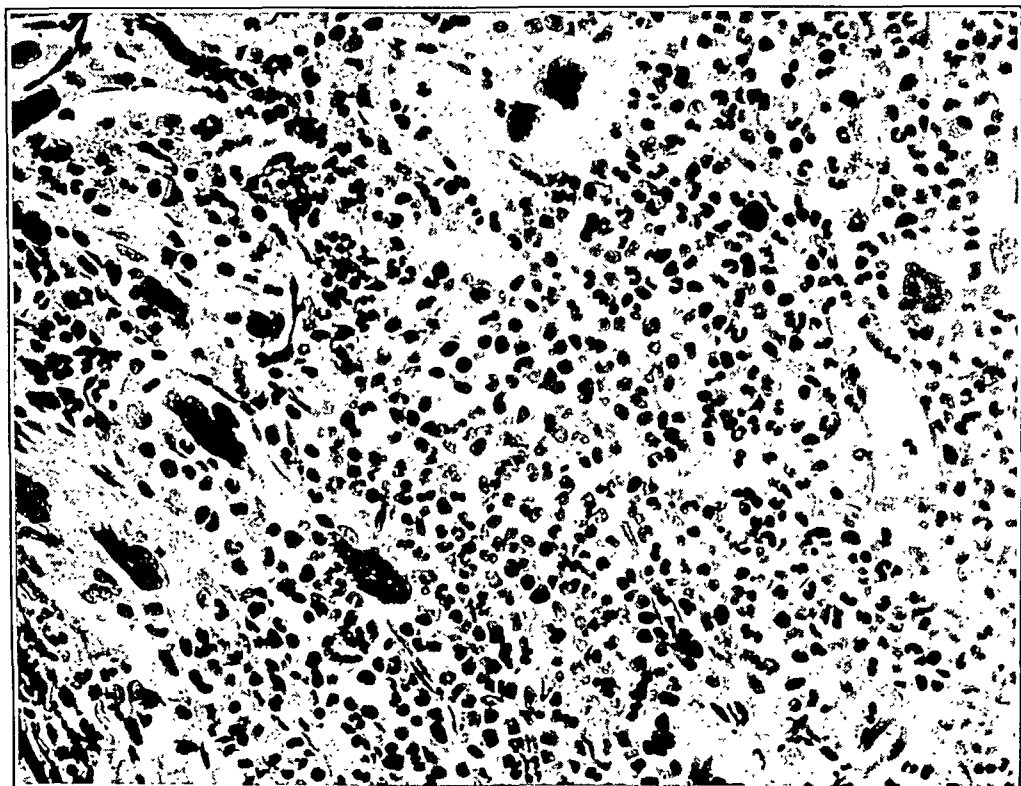


FIG. 1.—Bone-marrow biopsy showing numerous megakaryocytes and a preponderance of myeloid over erythroblastic elements. Note granulated eosinophilic myelocytes, especially in upper left corner. ($\times 300$.)

6 minims t.i.d., was taken for 2 weeks after discharge and then stopped. Following this, no medication was taken at any time.

The patient was not seen again until January, 1938, when she consulted the outpatient department. In April, 1937, she had visited another hospital for treatment of a small skin lesion on the tip of the nose, present continuously the past year, intermittently for 14 years. An epidermoid carcinoma of the skin of the nose was diagnosed. Following local Roentgen-ray therapy, the lesion rapidly healed without recurrence.

The patient thought herself to be in excellent health until July, 1937, when a painful, red swelling, which gradually increased in size and was most noticeable when the patient had been on her feet several hours, appeared on the medial aspect of the left leg. Occasionally, momentary sharp pain was noted to shoot from this region to the left abdomen. The patient thought her spleen had become firmer and possibly slightly smaller. She gave a history of two attacks of exquisitely tender, red swelling of a big toe, lasting several weeks; the right in the spring of 1936, the left in March, 1937. The patient herself diagnosed these attacks as "gout", but took no treatment. In January, 1938, physical examination in the outpatient department revealed pallor, splenomegaly and a painful red mass, 3 cm. in diameter, surrounded by indurated varicosities, on the medial side of the left leg. Anemia was present and the blood smear showed immature granulocytes (Table 1). Admission to the hospital was advised; but the patient preferred to wait until April 2, 1938, when she entered the medical service complaining of painful swelling of the left leg of 9 months' duration. During the 5-year interval there had been no significant weight change.

Physical examination on the second admission showed normal color of the lips, nail beds and retinae. The skin, gums and conjunctivae were slightly pale. The retinal vessels were not distended. The spleen was very firm, not tender and apparently the same size as previously described. The liver edge was palpable as before. Lymphadenopathy was absent. Bilateral saphenous varicosities extended to the thighs, more marked on the left. A red, elevated, slightly tender, circumscribed mass, 6 cm. in diameter, was present on the medial aspect of the midportion of the left leg. Several large, firm varicose veins radiated superiorly from this mass, which was indurated, apparently subcutaneous, not attached to bone, and surrounded by a moderate degree of venous congestion. Roentgen-ray examination of the left leg showed dilated tortuous veins, apparently subcutaneous, in the upper half. The bones appeared normal except for slight loss in detail, with slightly increased density, of the upper end of the tibial diaphysis. On the lateral aspect of the midportion of the right leg was a small black eschar, 0.5 cm. in diameter, not tender or indurated. No other skin lesions were present. No tophi were found in the ear cartilages, eyelids, hands, elbows or feet. Examination otherwise was as described on the first admission.

Laboratory studies (second admission). The urine sediment showed an occasional hyaline cast in one specimen; the specific gravity ranged up to 1.026. There was no Bence-Jones proteinuria. The stool examination was negative. The basal metabolic rate was +15% (DuBois standards). The repeated blood serology was negative. Icterus index was 8. Fragility test: patient's cells showed initial hemolysis in 0.46% NaCl, normal control cells in 0.44%. Blood uric acid: April 9, 5.3 mg. %; April 19, 5.1 mg. % (normal value is less than 4 mg. %).

Table 1 shows studies of the blood counts and smears.

Clinical course (second admission). The temperature (oral) was normal except from April 8 to 10, when there was an elevation to 99.8°. At this time the patient complained of acute pain in the right great toe and stated she thought she had "gout". Examination showed redness, swelling,

warmth and marked tenderness of the first right metatarsophalangeal joint. Hyperuricemia was present. Tincture of colchicum (4 cc. t.i.d.) was administered, and considerable relief of pain and tenderness occurred within 24 hours. A mild diarrhea was associated with the first 2 days of colchicum medication. Colchicine (0.0006 gm. t.i.d.) was substituted for tincture of colchicum from April 19 until discharge. Roentgen-ray examination of both feet (April 21) showed narrowing of the metatarsophalangeal joints of the great toes, with slight reaction in the bones. A small cystic area, similar to those seen in gout, was present at the distal end of the first phalanx of the left great toe, just beneath the articular surface. Two unsuccessful attempts were made to recover crystals of urate or calcium deposit from the mass on the medial side of the left leg.

On April 12, bone marrow biopsy was performed.* A segment of marrow, 0.5 cm. in diameter, was trephined from the midsternum at the level of the fourth rib, and fixed in Zenker's solution. On section (photomicrograph), the marrow showed almost no fat tissue, being filled with numerous myeloblasts and myelocytes. Megakaryocytes and erythropoietic cells were present in moderate numbers. The section was regarded as having the appearance typical of myelogenous leukemia.

The tender mass on the left leg gradually disappeared. No change was noted in the enlarged spleen. After relief of arthralgia, the patient was very comfortable, and on April 27, 1938, she was discharged, to be followed in the outpatient department, to continue iron therapy, and to apply a tensor leg bandage should the venous induration recur.

Comment. The association of leukemia and erythremia has been much discussed.^{3-5,7} During the course of erythremia a leukemic picture may develop; less frequently, the latter may precede polycythemia, and perhaps myelogenous leukemia may exhibit an initial polycythemic phase. The statement has been made³ that when the two conditions occur in the same patient, the case is probably leukemia rather than erythremia.

Possibly this variety in clinical pictures reflects the effect of one factor on different hematopoietic tissues. In erythremia the causative factor is unknown, but the bone marrow may exhibit hyperplasia, not alone of erythrocytic elements but of leukoblastic tissue and megakaryocytes as well. In fact, in long-continued erythremia with development of anemia very disorderly blood formation, including extramedullary hematopoiesis, may occur and be reflected in the peripheral blood picture.⁵

This "panmyelopathy" of erythremia may aid in the occasional complication of this condition by gout, if gout with leukemia is due to endogenous nuclear catabolism with subsequent hyperuricemia, as has been suggested.² Perhaps nuclear material from only the erythroblastic elements is a sufficient source for the increased blood uric acid.² Gout has been described separately with erythremia (Davis,¹ Parkes Weber,⁶ and others) and leukemia (Schultz,⁸ Vining and Thomson,⁹ and others), but to my knowledge no report has recorded both diseases with gout in 1 patient.

* I am indebted to Dr. W. Dameshek and Dr. S. Schwartz, Beth Israel Hospital, Boston, for supervision of this procedure and for pathological studies in collaboration with the Pathological Department, Peter Bent Brigham Hospital.

In the case presented, the subsequent course may determine the proper designation; for the present, the term "subleukemic myelosis" would seem acceptable.

Summary. Erythremia, gout, anemia and the blood smear and bone marrow characteristics of subleukemic myelosis occurred in a female patient observed during a 5-year period. The significance of this course of events is briefly discussed.

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THE MECHANISM OF THE COMPENSATORY CHANGES IN ANEMIA, ESPECIALLY AS REGARDS BLOOD CO₂ AND pH.

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THE various methods by which the body compensates for the diminishing oxygen-carrying power of blood with increasing anemia have been well worked out by many investigators. It is therefore surprising to find how little has been done to elucidate the mechanism by which CO₂ is removed from the tissues in this condition, at least in man. Increasing anemia means a diminished buffering power of blood, and therefore (unless there are compensatory measures) we would expect increasing difficulty in removing CO₂ from the tissues, *i. e.*, that the normal changes in tissue CO₂ tension would produce in the blood relatively small changes in CO₂ content and relatively great changes in pH. Barr and Peters² and Means *et al.*¹² have proved this by demonstrating that for CO₂ tensions above 15 to 20 mm. Hg the CO₂-dissociation curve of anemic blood is flatter (though often higher) than that for normal blood (Fig. 1). At tensions below 15 to 20 mm. Hg, however, as a glance at the figure will show, the curve must be considerably steeper, *i. e.*, the blood can take up larger volumes of CO₂ with smaller pH changes than normally.

The difficulty in removing CO₂ from the tissues by anemic blood might theoretically be compensated (*a*) by an increased volume of blood flow through the tissues, and (*b*) by such an increase in pulmonary ventilation as would reduce tissue and blood CO₂ tension

to about 15 or 20 mm. Hg, at which tension, as Figure 1 shows, we might expect normal amounts of CO_2 to be absorbed per unit change of CO_2 tension.

As regards the former, Dautrebande⁵ has shown that there is little or no increase of blood flow through the tissues until the hemoglobin content of blood falls to about 40%, beyond which the cardiac output rises rapidly. As regards the latter, however, we have little information.

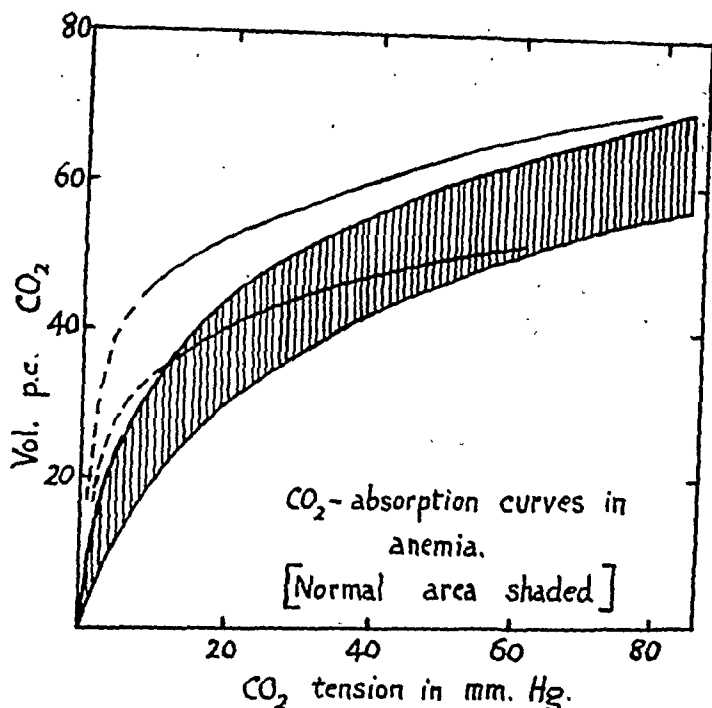


FIG. 1.—The CO_2 dissociation curves in normal and anemic bloods. The former fall in the shaded area, but the latter are higher and flatter, falling between the two higher curves. (Redrawn from Barr and Peters,² and Means *et al.*¹²)

To elucidate the mechanism of CO_2 removal we require data concerning the CO_2 tension and pH of the tissues. To obtain this data directly in man is hardly practicable, but we can obtain indirect information concerning the state of affairs in the tissues by an examination of the venous blood, which probably gives a truer picture of conditions in the tissues than does arterial blood, on account of the fact that there is a shift of water and salts from tissues to blood in the distal portions of the capillaries, *i. e.*, into venous blood, whereas in the proximal portions of the capillaries, the shift is in the opposite direction.

The facts at present are few. It is true that some workers have investigated the blood in animals after hemorrhagic anemia, but very little has been recorded in man. Smith *et al.*¹⁸ and Emerson

and Helmer⁶ found only slight changes in the CO_2 content of venous blood and plasma in 14 and 29 cases respectively of anemia, most of which were of the pernicious type, but Peters *et al.*¹⁵ found a definitely lower plasma CO_2 in 2 cases of secondary anemia. As regards pH, Means *et al.*¹² found a more alkaline arterial blood in 1 case each of pernicious anemia and leukemia, but a normal pH in 1 case of secondary anemia. Barr and Peters² also report a higher arterial pH in 2 cases of pernicious anemia but a normal pH in 1 of secondary anemia. Venous pH, however, appears to remain normal (Barr and Peters in 2 cases;² Peters and others¹⁵ in 2 cases, and Emerson and Helmer⁶ in 29 cases of pernicious anemia, but with a wide variation in the pH range).

On account of these meager facts and the small number of patients examined, we decided to investigate the venous blood over a wide range of hemoglobin variations.

Methods. The following estimations were made on blood drawn from the median-basilic vein, without loss of CO_2 , from 75 normal students and 57 patients with secondary anemia: *a*, Red cell or hematocrit volume (Shock and Hastings¹⁷); *b*, blood pH (Shock and Hastings¹⁷); *c*, plasma or blood CO_2 content (Van Slyke); *d*, the oxygen content in some cases (Van Slyke and Neill). The hematocrit and pH values are each the average of four readings, which rarely varied more than 0.5 and 0.05 respectively. The plasma CO_2 values were made in duplicate. In some additional cases arterial blood from the brachial or femoral artery was also examined.

A few figures from cases of polycythemia are included for their comparative interest.

All subjects were either in bed, or if not, were rested for 30 minutes after arrival at the laboratory for examination.

A parallel series of observations was made on dogs 48 hours after the production of a hemorrhagic anemia or a transfusion polycythemia. In the former, the blood was centrifuged and the plasma returned to the dogs. In the latter, red cells, with a minimum of saline only, were injected.

Results. *A. Venous Plasma CO_2 .* When the plasma CO_2 content is plotted against the red cell (hematocrit) content rather a wide scattering of points results. This, of course, is to be expected when we take into consideration the several influences affecting different individuals (see Discussion). When, however, we plot the average CO_2 figures for different groups arranged according to their red cell content, it is seen that increasing anemia results in a falling plasma CO_2 (Fig. 2, Curve *A*). For comparison, we have also added Curve *B*, representing the plasma CO_2 of arterial blood, calculated from figures by Shock and Hastings¹⁷ from healthy students, and therefore of limited range. The two curves are parallel, *i. e.*, the arteriovenous difference is constant over this short range. They both show a maximum value at a hematocrit reading of 50 to 55%.

Three patients were examined on from 3 to 6 occasions during recovery from anemia. All showed a steady rise of plasma CO_2 content.

If our polycythemia cases (E, F, G, H), together with 2 others (K, L) from Peters *et al.*,¹⁵ are at all typical, it would appear that in this condition the CO₂ curve falls again with increasing red cell content.

B. Venous Blood pH. When venous pH is plotted against red cell content, arranged as in *A*, although some scattering occurs, the average pH curve is found to fall slightly with increasing anemia and then to return to a fairly constant level of 7.34 (Fig. 2).

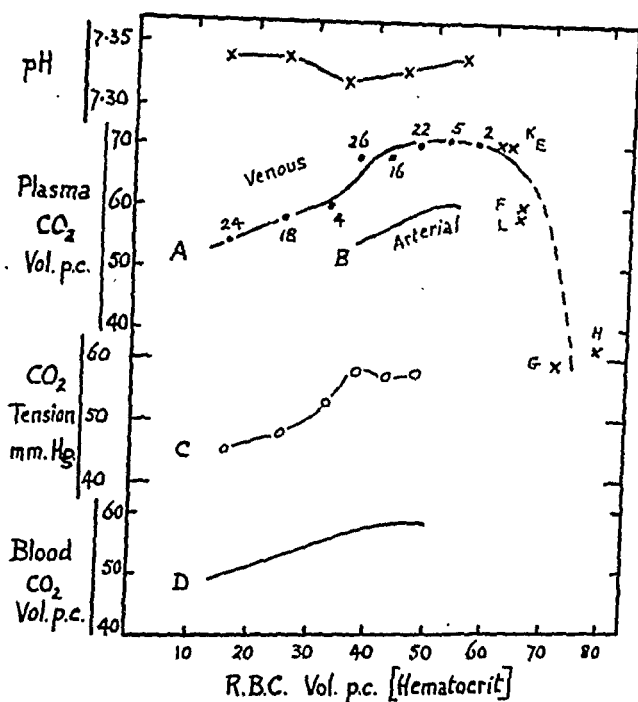


FIG. 2.—Showing the changes in pH, CO₂ content and CO₂ tension of venous plasma with increasing anemia. Each point on Curve A represents the average, and the adjacent figures the number of individuals, in each of the various groups.

C. Whole Blood, Arterial and Venous. In 17 cases, including 10 of the pernicious type, both arterial and venous bloods were also examined (Table 1 and Fig. 3). The outstanding findings are: 1, When the cases are arranged in descending order of hemoglobin or oxygen content it is found that below about 40% hemoglobin (8 cc. of oxygen per 100 cc. blood) there is a rapid fall in the arterio-venous oxygen difference (Fig. 3, *a*), which, as will be discussed later, is due to an increased blood flow through the tissues, and hence a smaller reduction of oxyhemoglobin per 100 cc. of blood. The relations of diminishing A-V oxygen difference (increasing blood flow) to A-V CO₂ difference and A-V pH difference are further shown in Figure 3, *b* and *3c*. 2, The average arterial pH is 7.38, which is close to that found by Shock and Hastings¹⁷ (whose method

we used) for normal people, *viz.*, 7.39 to 7.41. Although the A-V oxygen difference bears no relation to the absolute pH values, there appears to be a relationship to the A-V pH differences, which average 0.08, a figure much greater than the normal (0.02 to 0.03). 3, Whole blood CO₂ content is not appreciably affected by anemia, although when calculated from the data in Figure 2 a small fall with increasing anemia is found (Fig. 2, Curve D).

TABLE 1.—ARTERIAL AND VENOUS OXYGEN, CO₂ AND pH IN 17 CASES OF ANEMIA.
Cases Given as Cc. per 100 Cc. Blood.

Case.	Oxygen content.			Blood CO ₂ content.			pH.			Type of anemia.
	Arterial.	Venous.	Difference.	Arterial.	Venous.	Difference.	Arterial.	Venous.	Difference.	
1 . .	9.8	5.4	4.4	56.3	60.9	4.6	7.38	7.33	0.05	Pernicious.
2 . .	b8.2	2.4	5.8	55.7	59.1	3.4	7.35	7.24	0.11	Pernicious.
3 . .	8.0	2.3	5.7	49.7	54.2	4.5	7.46	7.36	0.10	Pernicious.
4 . .	c7.3	3.6	3.7	68.7	69.9	1.2	7.27	7.24	0.03	Pernicious.
5 . .	6.7	0.5	6.2	59.0	63.2	4.2	7.38	7.26	0.12	Secondary chronic.
6 . .	6.5	2.7	3.7	41.3	45.7	4.4				Pernicious.
7 . .	5.8	2.3	3.5	53.0	58.4	5.4	7.45	7.35	0.10	Cancer of colon.
8 . .	5.5	1.9	3.6							Secondary.
9 . .	5.4	2.3	3.1	42.4	45.2	2.8	7.39	7.34	0.05	Pernicious.
10 . .	4.3	0.7	3.6	56.1	57.8	1.7	7.40	7.28	0.12	Pernicious.
11 . .	b3.9	1.6	2.3	54.8	55.8	1.2	7.35	7.30	0.05	Pernicious.
12 . .	c3.8	0.7	3.1	56.8	58.3	1.5	7.40	7.33	0.07	Pernicious.
13 . .	3.8	1.3	2.5							Uremia.*
14 . .	3.5	2.8	0.7	46.6	50.0	3.4				Secondary, chronic.
15 . .	3.5	0.9	2.6							Pernicious.*
16 . .	a2.5	0.5	2.0				7.38	7.28	0.10	Carcinoma, stomach.
17 . .	a2.2	0.5	1.7				7.39	7.29	0.10	Carcinoma, stomach.

* Two cases taken from Harrop.⁸

Three cases were each examined twice. These are marked a.a., b.b., c.c.

TABLE 2.—VARIATIONS IN pH AND CO₂ CONTENT OF VENOUS BLOOD OF DOGS WITH VARIATIONS IN RED CELL CONTENT.

Hematocrit	10-20	21-40	41-60	61-76
Number of observations.	11	19	11	8
Average pH	7.275	7.30	7.33	7.315
Average CO ₂	49.6	50.4	49.6	54.1

D. Dogs. The results in dogs differ from those in man (Table 2). The pH curve for venous blood is lowest in severe anemia, rising to a maximum with normal red cell content. The venous CO₂ content, however, remains unchanged. These results are in keeping with those obtained after hemorrhage without anesthesia in dogs by Johnston and Wilson,⁹ Bennett,³ Milroy,¹³ Evans,⁷ and Riegall.¹⁶

Our few observations in polycythemia following transfusion in dogs indicate a falling pH and a rising CO₂ content of venous plasma.

Discussion. The CO₂ content of venous blood is at any one moment the resultant of many factors even in health, among which are metabolic rate, the ratio of pulmonary vital capacity to body weight (Apperly and Semmens¹), external temperature (Sundstroem¹⁹), physical fitness (Osman and Close¹⁴), and so forth.

In anemia, there are other possible factors, such as altered sensitiveness of the respiratory mechanism, increased rate of blood flow, perhaps tissue tolerance, and finally failure. Consequently, in any

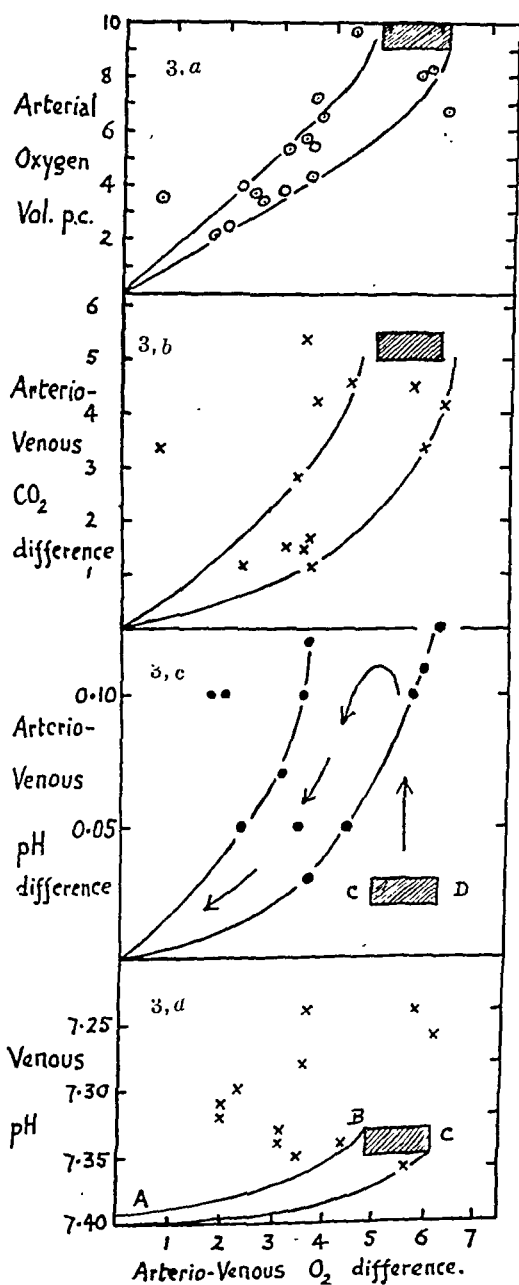


FIG. 3.—Showing the relationship of diminishing arteriovenous oxygen difference (increased blood flow through the tissues) to degree of anemia, (Fig. 3, a): arteriovenous CO_2 difference, (Fig. 3, b): arteriovenous pH difference, (Fig. 3, c): and venous pH, (Fig. 3, d). Normal ranges indicated by shaded areas.

attempt to correlate the final CO_2 content of the blood with any of these factors, considerable scattering must result. When the average of each group is taken however, as in Figure 2, the relationship of plasma CO_2 to varying red cell content of blood is clear. Further, when the CO_2 tension for each group or point on the curve is calculated from plasma CO_2 content and pH, a nearly parallel curve is obtained, indicating that with increasing anemia the CO_2 tension in the blood also falls (Fig. 2, Curve C).

If it be correct that the changes in venous blood are an index of tissue changes, then we also have a diminished CO_2 tension and alkali content of the tissues in anemia. This is in complete agreement with Campbell's⁴ direct observations of CO_2 tension in the tissues of rabbits in posthemorrhagic anemia.

What factors are responsible for this lower tissue CO_2 tension? Certainly it is not due to a diminished CO_2 production or to oxygen want, since it is well known that the arteriovenous oxygen difference is undiminished (down to a hemoglobin level of 40 to 50%) and that metabolism remains unchanged. (Metabolism may even rise slightly owing to increased cardiac and respiratory work when the anemia becomes severe.)

When with increasing anemia there is insufficient oxygen to maintain normal tension in the tissues, a compensatory opening up of more capillaries in the tissues occurs, thereby diminishing the distance over which oxygen has to diffuse to maintain oxygen pressure (Krogh¹⁰). This in turn means an increase of cardiac output, which occurs when hemoglobin falls to about 40 to 50% and increases rapidly with increasing anemia (Dautrebande⁵). The increasing blood flow through the tissues means that less and less oxygen will be removed from each unit of blood, *i. e.*, with increasing anemia the arteriovenous oxygen difference diminishes (Fig. 3, *a*). This has also been shown by Harrop⁸ and by Liljestrand and Senstrom.¹¹

Using the diminishing arteriovenous oxygen difference as a measure of increasing blood flow, we next investigated the relationship of arteriovenous oxygen difference to arteriovenous CO_2 difference and pH difference (Fig. 3, *b* and 3, *c*). It will be seen that with increasing blood flow through the tissues (falling A-V O_2 difference) there is also a fall from the normal A-V CO_2 difference (5 to 5.4 vols. %) and a fall in the A-V pH difference, *i. e.*, the venous blood more and more resembles arterial blood. This in turn means that the venous blood CO_2 and plasma CO_2 contents steadily fall without necessarily involving any increase of pulmonary ventilation.

When, however, we similarly plot the A-V O_2 difference against venous pH we find that all pH figures fall considerably below the area A B C (Fig. 3, *d*) into which they should theoretically fall if venous pH changes were merely due to increased blood flow through

the tissues. Further, many of the A-V pH differences are considerably greater than the normal figure (0.02 to 0.03). The reasons for these differences are shown in Figure 4 in which both the arterial and venous blood CO₂ figures are plotted. The line A B represents the shift in CO₂ tension, content and pH when normal arterial blood changes to the venous condition. In the anemia cases, however, although the shift in CO₂ content is less than normal (see also Fig. 3, b), the shift in both CO₂ tension and pH of the group as a whole is considerably greater than normal. In other words, with increasing anemia and therefore diminishing buffering power, greater and still greater increases of CO₂ tension are necessary to make arterial blood take up its normal amount of CO₂. The H-ion concentration, therefore, must also steadily rise (see also the early pH fall in Figure 2).

This brings us back to a consideration of Figure 3, c. The normal A-V oxygen difference is 5 to 6 vols. % and the pH difference 0.02 to 0.03. These facts are represented by the area C D. With increasing anemia down to 40 to 50% hemoglobin there is an increasing difficulty in taking up CO₂ and consequently a rising CO₂ tension and H-ion concentration in both tissues and venous blood, with increasing A-V pH difference, although the A-V oxygen difference remains unchanged. At and below 40 to 50% hemoglobin (8 to 10 cc. oxygen %), however, there is an opening up of capillaries and an increased blood flow. The venous blood then comes increasingly to resemble arterial blood and the large A-V pH difference now falls rapidly. The rise and fall of pH difference is represented by the arrows in Figure 3, c. From this it would appear that rising CO₂ tension and pH difference precede the opening up and dilatation of capillaries, and suggest a causal relationship. This is supported by the figures in Case 4, which has the highest arterial and venous CO₂ and the lowest pH; *i. e.*, a CO₂ acidemia (? cause). These are accompanied by a low A-V oxygen difference and the lowest A-V CO₂ and A-V pH differences in the series, *i. e.*, one of the greatest increases in tissue blood flow. The rising H-ion concentration might also be expected to result in pulmonary hyperventilation, a fall in alveolar CO₂ tension (reported by some authors but indicated in only some of our arterial blood figures in Figure 4) and the falling plasma CO₂ content seen in Figure 2. The diminishing plasma CO₂, therefore, is due to the two factors, *viz.*, hyperventilation and increased blood flow.

One or two items among our figures are of interest:

Nearly all cases have higher arterial and venous CO₂ contents than the average normal, or at least they lie in the high normal area (Fig. 4). Although undoubtedly largely due to the relatively greater proportion of plasma (which holds more CO₂ than corpuscles) in anemic blood, there must be some other factor, since the blood CO₂ content does not vary as exactly as we would expect with the

relative volume of plasma (or inversely as the degree of anemia). These facts have also been noted by others.^{2,12} The variation of the pH over a range much wider than normal has been commented upon by Emerson and Helmer,⁶ although they offered no explanation thereof.

The diminution of the A-V CO_2 difference is rather more marked than normal compared with the A-V oxygen difference, giving a R.Q. (respiratory quotient) of 0.84. Many cases, indeed, have as low an R.Q. as is found in diabetic acidosis, which suggests the presence of lactic or other acid in these severe anemias. Most

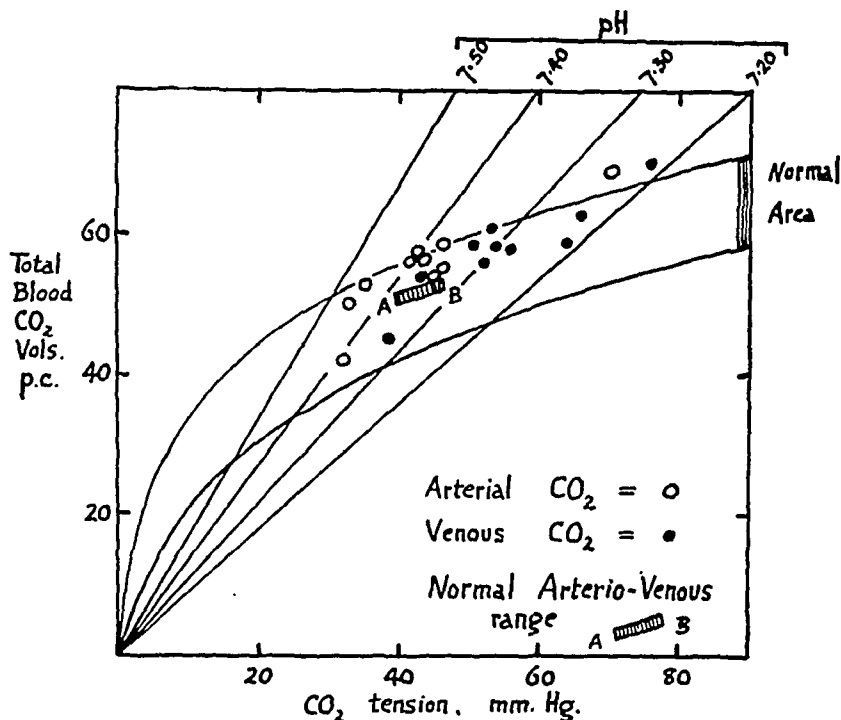


FIG. 4.—Showing the shift from arterial to venous pH, CO_2 content and CO_2 tension in 10 cases of anemia, compared with the shift in normal blood (area A B).

authors, however, deny any lowering of R.Q. in anemia, *e. g.*, in Harrop's 10 cases the R.Q. was 0.93.⁸ Of course, one must also bear in mind that venous blood even normally varies widely in different veins, and we cannot assume that blood from the arm is representative of the venous blood as a whole.

In our dog experiments (Table 2) the falling pH but level plasma CO_2 curve support our general conclusion that anemia leads primarily to a rising H-ion concentration. The compensatory increase of blood flow in man, by which rising H-ion concentration and CO_2 tension are prevented from rising still higher, does not, however,

appear to occur in dogs, since the pH continues to fall in the latter and the plasma CO_2 content remains at a steady level.

As regards our few cases of polycythemia, the data are too few to allow us to arrive at any conclusion concerning the underlying mechanism, although the falling plasma CO_2 is no doubt immediately due to the obvious dyspnea seen in these patients. It is of interest to note, however, that just as Campbell⁴ found a steadily diminishing CO_2 tension in the tissues of rabbits more or less parallel with the fall of hemoglobin content below normal (referred to above), so in the polycythemia following transfusion he also found a falling tissue CO_2 tension. These experiments together with our findings suggest that the same conditions are present in man.

Summary. 1. Beyond a few isolated facts there is not, so far as we know, any complete study of the relations between blood CO_2 , pH and oxygen in anemia, nor of the methods by which the body rids itself of CO_2 in this condition.

2. In a group comprising anemias of various types we found, with increasing anemia, that:

A. Plasma CO_2 falls at first more rapidly and then more slowly. Whole blood CO_2 , however, remains practically unchanged.

B. Venous pH falls at first but later returns to normal. Arterial pH, however, remains normal.

C. The arteriovenous oxygen, CO_2 and pH differences, though little affected until the hemoglobin falls to about 40%, thereafter fall rapidly.

3. These changes are interpreted as indicating that:

A. In the less severe anemias (down to about 40% hemoglobin) rising hydrogen-ion concentration of venous blood, brought about by diminishing buffering power of blood, leads to some hyperventilation, with fall of plasma CO_2 and restoration of arterial pH.

B. In the more severe anemias (less than about 40% hemoglobin) the earlier rise of hydrogen-ion concentration has directly or indirectly brought about a greater blood flow through the tissues, so that the differences between arterial and venous oxygen, CO_2 , and pH diminish, thus lowering tissue CO_2 tension but sparing the respiratory mechanism.

4. Observations on dogs support 3A above, but indicate that 3B operates to a less extent than in man.

5. In a few cases of polycythemia, the plasma CO_2 falls rapidly with rise of red cell content.

6. In anemia, the respiratory quotient, as calculated from blood oxygen and CO_2 contents, is within normal limits.

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THE BLOOD PLASMA ASCORBIC ACID IN PATIENTS WITH ACHLORHYDRIA (PERNICIOUS AND IRON DEFICIENCY ANEMIA).*

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A NUMBER of studies reported in the literature suggest that achlorhydria might be a predisposing factor in the cause of vitamin C deficiency. The diagnosis of hypovitaminosis-C in patients with achlorhydria has been based on: 1, symptomatology;^{6,9,11,14} 2, increased capillary fragility;^{3,5,15,16} 3, decreased urinary excretion of ascorbic acid following ingestion of the vitamin;² or, 4, a decreased ascorbic acid level in the blood.¹² In the last study, performed in Denmark, the blood ascorbic acid averaged 0.20 mg. per 100 cc. in achlorhydric patients as compared to 0.30 mg. per 100 cc. in normal individuals. These values are lower than those usually encountered in this country. In order to obtain further information on this problem, we determined the reduced ascorbic acid of blood plasma in a group of patients with achlorhydria associated with pernicious or iron deficiency anemia. The results in general seem to confirm the hypothesis that a relationship exists between achlorhydria and vitamin C deficiency.

Procedure. The subjects consisted of 44 clinic patients on whom a diagnosis of pernicious or iron deficiency anemia had been made previously. The presence of complete achlorhydria had been established in practically all cases by the histamine fractional gastric analysis (exceptions noted in

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TABLE 1.—BLOOD PLASMA ASCORBIC ACID VALUES IN NORMAL INDIVIDUALS AND IN PATIENTS WITH ACHLORHYDRIA.

Normals.				Pernicious anemia.				Iron deficiency anemia.							
Name.	Age.	Sex.	Ascorbic acid, mg. per 100 cc. plasma.	Name.	Age.	Sex.	R.B.C., mil. per c.mm.§	Hgb., gm. per 100 cc.	Ascorbic acid, mg. per 100 cc. plasma.	Name.	Age.	Sex.	R.B.C., mil. per c.mm.§	Hgb., gm. per 100 cc.	Ascorbic acid, mg. per 100 cc. plasma.
Adequate Intake of Vitamin C.															
A. S.	63	F	1.08	S. P.*	67	F	5.24	15.7	0.52	L. B.†	43	F	5.11	15.3	0.44
L. F.	50	F	0.84	G. J.	45	M	5.12	16.6	0.40	H. N.	42	F	5.21	15.0	0.48
M. L.	47	F	0.80	M. D.	73	F	4.85	14.9	0.56	H. B.	49	F	4.80	14.8	1.16
S. H.	47	F	1.20	G. Y.	61	F	4.72	12.5	0.51	J. S.†	44	F	5.27	14.2	0.92
A. F.	47	F	0.72	F. W.	63	F	4.70	12.0	0.72	J. W.	44	F	4.62	14.0	0.63
E. E.	45	F	0.86	C. N.	73	M	4.60	14.4	0.40	S. N.	52	F	4.80	11.8	0.48
S. T.	40	F	1.00	M. S.	53	F	4.49	16.1	0.40	E. L.§	40	F	4.77	11.6	0.40
S. A.	53	F	0.84	E. H.	60	F	4.33	14.5	0.46	C. C.	46	F	3.92	9.0	1.11
C. H.	46	F	0.80	V. T.	42	F	4.19	13.4	0.80	K. T.	52	F	4.68	8.2	0.64
V. M.	45	F	1.00	E. R.	69	F	4.11	11.2	0.92	V. G.	21	F	3.89	7.6	0.77
F. H.	61	M	0.88	J. M.	50	F	3.91	15.4	0.64	E. K.	47	F	3.85	7.6	0.97
W. M.	59	M	0.64	J. S.	66	M	3.88	14.2	0.48						
W. R.	47	M	0.80	B. F.	69	F	3.88	12.4	0.44						
L. C.	45	M	0.68	K. K.	63	F	3.79	12.5	0.60						
J. H.	44	M	0.96	F. C.	45	F	3.76	12.3	0.52						
				A. L.	66	F	3.45	10.7	0.72						
Mean			0.87 ± 0.03						0.57 ± 0.03						0.73 ± 0.06
D/PED*			..						7.5						2.3
Inadequate Intake of Vitamin C.															
K. L.	69	F	0.53	P. C.	41	F	4.98	12.4	0.64	E. P.	32	F	4.73	14.0	0.32
E. S.	48	F	0.80	M. M.	64	F	4.87	13.3	0.52	V. L.	65	M	5.37	13.8	0.60
T. C.	63	M	0.44	J. B.	50	F	4.75	14.7	0.40	A. S.	43	F	4.94	13.4	0.56
C. T.	53	M	0.58	F. F.	43	M	4.35	15.1	0.32	M. C.	23	F	4.68	12.8	0.34
P. L.	52	M	0.48	E. S.	46	M	3.91	15.2	0.68	J. C.*	67	M	4.40	12.3	0.32
M. D.	49	M	0.82	R. S.	54	M	3.23	13.8	0.54	W. W.	41	M	5.16	12.3	0.40
J. G.	42	M	0.56	H. J.	50	M	2.78	10.5	0.40	A. G.*	46	F	5.40	12.1	0.56
V. G.	41	M	0.92	E. A.	76	M	2.30	9.0	0.24	L. C.	47	F	3.98	12.1	0.55
S. K.	48	M	0.64							J. M.	45	M	5.18	10.3	0.40
Mean			0.64 ± 0.04						0.47 ± 0.03						0.45 ± 0.03
D/PED*			..						3.4						3.8

* Ewald meal.

† - Maximum HCl = 4 units

‡ - Maximum HCl = 5 units

§ - Maximum HCl = 14 units

× Difference of means

Probable error of difference of means

Cases included in series as low values with histamine stimulation probably represent a functional achlorhydria.

Results considered to vary significantly from normal when ratio is greater than 3.

table). The therapy and the erythrocyte counts and hemoglobins at the time of the tests were variable. Among the patients with a normal blood picture, those of the pernicious anemia group were usually receiving parenteral liver therapy, while those of the iron deficiency anemia* group were receiving or had received iron therapy. Patients with subnormal erythrocyte counts or hemoglobins had received: 1, no previous therapy; 2, no recent therapy; or, 3, inadequate recent therapy. No determinations made during active remission with liver or iron therapy are included in the table. Control observations were made on 24 clinic patients who exhibited no evidence of systemic disease. The diet of each subject was evaluated as accurately as possible and classified as being adequate or inadequate in ascorbic acid. Less than 30 mg. per day were regarded as inadequate. Determinations of the reduced ascorbic acid were made on blood plasma by the micromethod of Farmer and Abt.⁴ Blood specimens were drawn 3 to 4 hours after a breakfast or lunch that contained no citrus fruit. Normally, the ingestion of moderate amounts of vitamin C in a meal has little effect on the plasma level after this interval of time. This is shown by the following observations. The fasting plasma ascorbic acid was determined in 6 normal individuals and a breakfast including 150 to 200 cc. orange juice (75–100 mg. ascorbic acid) was then taken. Within 3 hours after the meal, the plasma ascorbic acid had returned to the fasting level.

Results. (See Table 1.) When the diets were adequate in vitamin C, the control group had a mean plasma ascorbic acid level of 0.87 mg. per 100 cc., which falls within the normal range (0.7–1.5 mg. per 100 cc.).¹ Patients with pernicious anemia receiving an adequate diet had a mean ascorbic acid of 0.57 mg. per 100 cc.. This decrease from the normal is statistically significant. A similar decrease was not exhibited by the patients with iron deficiency anemia. Although many low values occurred in this group, the mean value of 0.73 mg. per 100 cc. is not significantly lower than the normal. When the diets were inadequate in vitamin C, the controls had a mean plasma ascorbic acid of 0.64 mg. per 100 cc. as compared to 0.47 and 0.45 mg. per 100 cc. in the pernicious anemia and iron deficiency anemia groups, respectively. The latter values are both significantly lower than the normal.

In order to confirm the assumption that the low plasma ascorbic acid values were an index of hypovitaminosis-C, an excretory test was performed on 2 patients with pernicious anemia, both of whom had plasma ascorbic acid values of 0.56 mg. per 100 cc. Following the intravenous injection of 100 mg. ascorbic acid, a urinary excretion of 2.7 and 8.9 mg., respectively, occurred during the next 3 hours. These values fall within the range observed by Ralli *et al.*¹³ in patients with vitamin C subnutrition.

The plasma ascorbic acid values in patients with pernicious and iron deficiency anemia in complete remission were comparable to the values in similar patients with decreased erythrocyte counts or hemoglobins (Table 1). Several patients studied repeatedly during

* The term iron deficiency anemia is used even though the patient has recovered from the anemia.

early remission with liver or iron therapy showed no consistent variations in the plasma ascorbic acid level.

The results obtained suggest that achlorhydria might be a factor in decreasing the assimilation of ascorbic acid. This was especially true when the diets were inadequate, as patients with iron deficiency anemia receiving adequate diets did not have a significantly depressed mean plasma ascorbic acid. The lower ascorbic acid values observed in patients with pernicious anemia receiving adequate diets might be partially explained by factors outside of achlorhydria, e. g., malabsorption.

Attempts to Explain Why Achlorhydria Might be Associated With a Decreased Assimilation of Ascorbic Acid. Vitamin C deficiency in patients with achlorhydria has been variously ascribed to: 1, increased destruction of ascorbic acid in non-acid gastric juice;⁵ 2, increased destruction of the vitamin by bacteria present in the small intestine;² and, 3, decreased absorption of ascorbic acid due to changes in the gastro-intestinal tract.⁵ An attempt has been made to gain information on the importance of the above factors.

It is known that ascorbic acid becomes increasingly labile as the alkalinity of the medium is raised. For comparative purposes 10 mg. ascorbic acid were incubated in buffer solutions of varying pH's for 3 hours. At pH 1.45, which falls in the range of normal gastric juice, 14% destruction of the vitamin occurred. At pH 7.95, which represents achlorhydric juice,⁸ there was 65% destruction during the same period. Under identical conditions, ascorbic acid was incubated in specimens of normal gastric juice (pH 1.25-2.1) obtained from 13 individuals after an alcohol* or Ewald meal. The destruction of ascorbic acid during a 3-hour period was inconstant and varied from 29 to 81%. The per cent destruction in achlorhydric juice was similar to that observed in the alkaline buffer solutions. There is no apparent explanation for the difference in the destruction of ascorbic acid in acid gastric juice and that occurring in buffer solutions of the same pH.

Bacteria are plentiful in the upper small intestine and stomach of individuals with achlorhydria.¹⁸ Cultures of *B. coli*, *Staph. albus*, *B. welchii* and enterococcus were made from the duodenal contents and feces of 2 patients with pernicious anemia. Living suspensions of the above organisms incubated with ascorbic acid for 3 hours showed no destructive action on the vitamin. Bacteria having such a destructive action have been isolated recently from the gastric contents and feces of achlorhydric patients by Kendall and Chinn.^{10a,b} They have shown that the ability to destroy ascorbic acid is the property of a particular strain of organism rather than a generic characteristic.

* Alcohol *per se* had no destructive action on ascorbic acid, nor did it interfere with the determination.

The presence of malabsorption in patients with pernicious anemia and achlorhydric anemia has been demonstrated previously.^{7,17} To test the rate of absorption of ascorbic acid, 10 mg. per kilo were given by mouth to 6 patients with pernicious anemia and to 6 normal individuals. Blood plasma ascorbic acid determinations were made at hourly intervals. In the normals, the plasma ascorbic acid increased to a level of 1.6 to 2.7 mg. within 2 hours. Five of the patients with pernicious anemia showed normal curves. In the sixth case, the curve was practically flat, the value not exceeding 0.6 mg. per 100 cc. It is of interest that this patient did not show a normal blood value even after continued ingestion of vitamin C in liberal quantities. These observations suggest that malabsorption of ascorbic acid was a factor in at least 1 patient with pernicious anemia.

None of the above experiments establishes a single explanation for an association of vitamin C deficiency with achlorhydria. Possibly a combination of such factors as lack of an acid gastric juice, bacterial growth, and malabsorption might be sufficient to interfere with the assimilation of ascorbic acid in the patient with achlorhydria associated with pernicious or iron deficiency anemia.

Summary. The blood plasma ascorbic acid was determined in 44 patients with achlorhydria associated with pernicious or iron deficiency anemia in remission or relapse, and in 24 controls. With diets adequate in vitamin C, the mean blood ascorbic acid was significantly decreased from the normal in the patients with pernicious anemia, but not in the iron deficiency anemia group. With diets inadequate in vitamin C, the plasma ascorbic acid was significantly decreased from the controls in both the pernicious and iron deficiency anemia groups. The plasma ascorbic acid values showed no correlation with the erythrocyte counts and hemoglobins. Experiments were performed in an attempt to explain why there might be an association between vitamin C deficiency and achlorhydria.

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FATAL BACTERIAL ENDOCARDITIS DUE TO
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IN recent years it has become apparent that *Salmonella suispestifer* is a not infrequent pathogenic organism for man. The literature on human infection has been comprehensively reviewed by Harvey.⁷ Although localized lesions in various organs have been described, no well-authenticated cases of bacterial endocarditis have been reported. This paper presents 2 such cases.

The organism belongs to the colon-typhoid group, and can be differentiated from *S. paratyphoid B* by its failure to ferment arabinose, trehalose, and inositol. By fermentation reactions and serologic studies *S. suispestifer* may be divided into two types, the American and the European. The European type differs from the American in forming hydrogen sulphide on lead acetate medium. Andrewes and Neave¹ showed that the American type (diphaseic type or Group I) contains two types of antigen: one, non-specific and common to both types; the other, specific for the American type. Organisms of the European type (monophasic type or Group II) contain only the non-specific antigen.

The diagnosis of *suispestifer* infection in man is usually made by culture of the organism from either the blood stream or a local inflammatory lesion. Though readily identified by complete cultural studies, it may be mistakenly identified as *S. paratyphoid B*, if fermentations are done with only a small number of sugars. It seems highly probable that if each organism isolated as *S. paratyphoid B* were tested for the fermentation of arabinose, trehalose, and inositol, some of these would be shown to be *S. suispestifer*. As the antigenic properties of these two organisms overlap, and *S. suispestifer* may be agglutinated by *S. paratyphoid B* antiserum, this test is unreliable for identification purposes. As a diagnostic measure in cases of *S. suispestifer* infection where the organism is not recovered by culture, the demonstration of agglutinins in the patient's serum is of some value; particularly if a rising agglutination titer is found during the period of observation.

In man two separate and distinct types of infection by this organism have been encountered: first, acute outbreaks of food poisoning with symptoms referable to the gastro-intestinal tract,^{4,8,13} a type of infection which frequently occurs in epidemics and runs a rapid course of short duration with a low mortality rate; second, a febrile illness associated with invasion of the blood stream. It is

with the latter type of case that this report is concerned. Frequently the resultant picture is not unlike typhoid fever; but in numerous cases a metastatic focus is set up in a distant region of the body, the portal of entry rarely being recognized. Pyarthrosis,^{9b,11,16} osteomyelitis,^{9b,16} splenic abscess,¹⁵ infected fibroids,⁶ meningitis,^{9a} gall bladder inflammation,¹⁵ pneumonia,³ and cystitis^{9b} have been reported with *S. suipestifer* as the etiologic agent.

In a review of the literature the author has found no case of proven endocarditis due to this organism, although 2 cases have been reported which may possibly represent *S. suipestifer* endocarditis.^{5,14} In the Cincinnati General Hospital during a period of several months 2 cases of bacterial endocarditis were observed in which there is good evidence that *S. suipestifer* was the causative agent. It is believed that these cases should be reported in some detail.

Case Reports. CASE 1. Hosp. No. 81519. P. L., a 47-year-old colored male, entered the medical service October 27, 1937, complaining of generalized weakness and shortness of breath of 10 days' duration. His general health had always been good. There was no history of rheumatic fever, chorea, frequent upper respiratory infections, or syphilis. While at work 10 days before entry, he suddenly became weak and short of breath and from then on remained at home because of weakness and sweats, suffering a dull discomfort in his epigastrium and vomiting several times daily. There were no chills, diarrhea, or urinary symptoms. On the day of entry he had a transient period of unconsciousness lasting several minutes. He has received no medication. Physical examination revealed a well-developed and well-nourished colored male. The temperature was 100° F., pulse rate 64 per minute, and respiratory rate 26 per minute. The pupils were round, regular, and equal, but reacted poorly to light and during accommodation. The neck veins were moderately engorged and exhibited regular pulsations about twice as frequent as the arterial pulse. The lungs were clear. The heart was enlarged to percussion and the transverse dullness in the 2d interspace was 7 cm. The heart sounds were loud, of good quality, and A2 was greater than P2. A soft systolic murmur was heard within the apex and several observers heard also a soft, blowing, early diastolic murmur along the left sternal border. The rhythm was regular. The sounds associated with auricular contraction were not heard. The radial pulses were equal, synchronous, and of Corrigan quality. The blood pressure was 180/60 mm. of Hg. The liver edge was felt 3 cm. below the costal margin. The spleen was not palpated. An old scar about 5 mm. in diameter was present on the upper portion of the glans penis. Vibratory perception in the left leg was impaired and movements of coördination poorly performed.

The erythrocytes numbered 5,020,000 per c.mm. and the leukocytes 11,400. The hemoglobin content of the blood was 14.2 gm. per 100 cc. The differential leukocyte count showed 85% neutrophils, 12% lymphocytes, 2% monocytes, and 1% eosinophils. The urine contained a trace of albumin, an occasional leukocyte, and had a specific gravity of 1.031. The blood Kahn test was 2+. A lumbar puncture showed clear, colorless fluid with 18 lymphocytes per c.mm. and a protein content of 28 mg. %. The spinal fluid Wassermann test was 3+, and the colloidal gold curve 555531000. The electrocardiogram on entry showed complete heart block.

On the ward, the patient ran a febrile course. The systolic murmur became much louder and could be heard over the entire precordium but

was not transmitted to the neck. No petechiæ or embolic phenomena were noted. The leukocyte count rose to a peak of 33,400 per c.mm. Three blood cultures taken on the 3d and 4th days after admission were positive for *S. suipestifer*. On the 4th day the cardiac rhythm changed from complete heart block to sinus mechanism with partial heart block. The P-R interval was 0.40 second. Six days after entry the patient's condition appeared about the same except that large numbers of pus cells appeared in the urine. Suddenly, late in the afternoon of the 6th hospital day, he became extremely apprehensive, the pulse varied from 70 to 120, and he died within 5 minutes.

The *clinical diagnoses* were: septicemia due to *S. suipestifer* with probable acute bacterial endocarditis of the mitral valve, syphilitic heart disease with aortitis and aortic regurgitation, complete heart block, and central nervous system syphilis of the parietic type.

Necropsy (19 hours postmortem, by Dr. Ritterhoff). The heart weighed 840 gm. and was moderately dilated in all its chambers. The right ventricle was 4 mm. thick; the left, 17 mm. A reddish-yellow, granular, friable vegetation approximately 1 cm. in diameter was encountered on the mural endocardium of the right atrium just above the posterior tricuspid leaflet (Fig. 1). The vegetation was surrounded by an inflammatory reaction which extended into the atrial and ventricular musculature and was continuous with another vegetation on the endocardial surface of the left ventricle just inferior to the posterior cusp of the aortic valve. A small patent sinus was found to connect the two vegetations. Neither the tricuspid nor the aortic valve leaflet was involved by the inflammatory process. Sections through the inflammatory reaction selected to include both vegetations and the septal tissue between, showed extensive acute suppuration with piling up of thrombi at each end of the sinus tract. Many clusters of Gram-negative bacilli were seen throughout the inflammatory process and a culture from one of the vegetations revealed *S. suipestifer*. At the mid-portion of the sinus tract where it passed through the septum, the acute inflammatory reaction was surrounded by a zone of active fibroblastic and vascular endothelial proliferation heavily infiltrated with inflammatory cells, predominantly lymphocytes. This reaction extended upward and appeared to be continuous with a similar process in the media of the aorta in the region of its origin. Although *Treponemata pallida* were not demonstrated in sections prepared by the Levaditi method, the reaction was interpreted as due to syphilis. The ascending aortic arch was dilated and the intima presented extensive, fine longitudinal wrinkling and numerous yellow and pearl-grey plaques. The semilunar cusps of the aortic valve showed rolled edges and widening of the commissures. The coronary arteries were patent throughout their trunks and main divisions and their ostia were of normal caliber. The spleen weighed 350 gm. and contained several dark-red areas of infarction. The liver weighed 2750 gm. and had prominent vascular markings. The kidneys together weighed 475 gm. Thin yellowish-green pus was present in the intravesical portion of the ureters and there was marked injection about the trigone of the bladder. The brain weighed 1140 gm. and was covered by a thickened, opaque pia-arachnoid.

Anatomic Diagnoses. Syphilitic aortitis with extension to the myocardium; acute ulcerative mural endocarditis; moderate coronary arteriosclerosis and myocardial fibrosis; chronic passive congestion of the viscera; chronic active perihepatitis and intrahepatic cholangitis; acute splenitis; early acute cystitis, ureteritis, and pyelitis; cerebral gliosis, and chronic active leptomeningitis.

CASE 2. Hosp. No. 82809. D. W., a 31-year-old white male laborer, was admitted to the medical service on Nov. 24, 1937. At this time he was

too ill to give a history but subsequently it was learned that he had been confined to bed for several months at the age of 10 because of fever and migratory polyarthrititis. For the past 5 years he had noted mild dyspnea on exertion. Eight weeks before entry he contracted a head cold accompanied by a non-productive cough which forced him to leave his work. From this time on he became weaker, more dyspneic, and had numerous chilly sensations and night sweats. For 6 weeks he had been conscious of his heart beating rapidly. Four weeks before entry he began to expectorate reddish-brown, sticky material and soon thereafter experienced a pleural type of pain in the left chest. At this time he noted swelling of his legs.

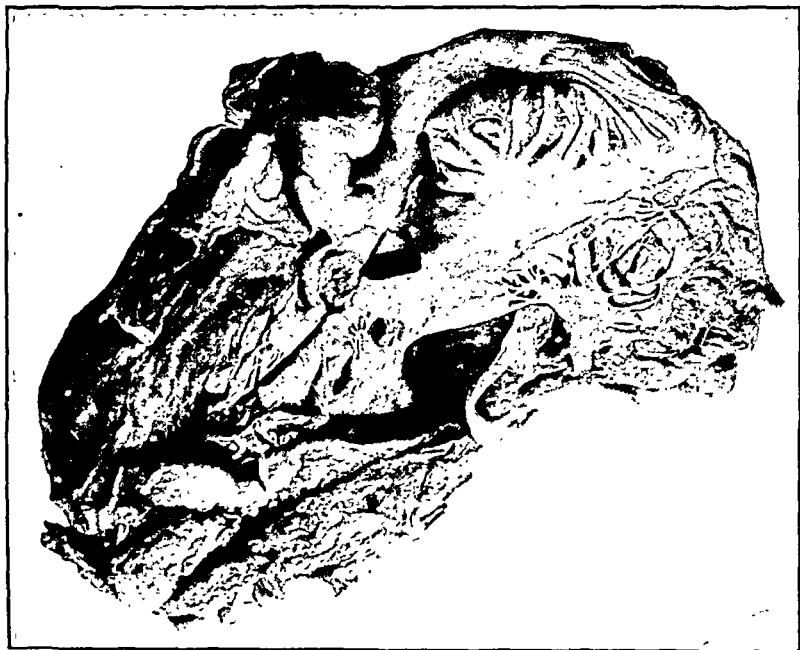


Fig. 1.—Right side of heart of Case 1; broad, tailless arrow in center of figure points to vegetative lesion superior to the posterior tricuspid leaflet. The vegetative process passes through the interventricular septum to reach the left ventricle just below the aortic valve.

On admission, the patient appeared moribund. The rectal temperature was 99.8° F., and the respiratory rate was 46 per minute. Neither the pulse nor the blood pressure could be obtained in the arms or the legs. The patient was orthopneic, cyanotic, and very restless. The thorax was symmetrical and there was evidence of partial consolidation at the base of the left lung with medium râles at the right base. The heart was enlarged both to the left and the right; sounds were of fair quality and systolic and diastolic murmurs were heard within the apex. The cardiac rhythm was totally irregular with an apical rate of 140 per minute. The liver was enlarged and tender. The spleen was not felt and there was no evidence of ascites. There was moderate edema of the lower legs. The fingers were not clubbed and no Osler's nodes were present. The entire left arm was slightly edematous and the left side of the neck and the left supraclavicular fossa somewhat swollen.

The erythrocytes numbered 5,540,000 per c.mm. and the leukocytes 16,000. The hemoglobin content of the blood was 13.4 gm. per 100 cc. The differential leukocyte count showed 78% neutrophils, 17% lymphocytes, 3% monocytes, 1% eosinophils, and 1% basophils. The urine con-

tained a trace of albumin and had a specific gravity of 1.016. The blood Kahn test was negative and the blood urea nitrogen 11 mg. %. The electrocardiogram showed a rate of 150 per minute, auricular fibrillation, right axis deviation, and changes suggesting myocardial damage.

On the ward, the patient was given ouabain intravenously, followed by digitalis by mouth; and shortly his blood pressure was obtained at 100/70 mm. of Hg, at which level it remained throughout his hospital stay. The apical rate was adequately slowed but he failed to improve. The edema of the left arm and the left side of the neck became more marked, and tender cordlike axillary and external jugular veins became palpable on this side. Within a few days superficial collateral veins were observed over the left upper arm and thorax with the direction of blood flow toward the midline. The patient had a spiking temperature with peaks as high as 105° F. and occasional chills. Icterus became apparent on his 2d hospital day and progressed thereafter; the icteric indices on the 2d, 13th, and 16th hospital days were 39, 77, and 91 respectively. The urine contained both bilirubin and urobilinogen, van den Bergh tests showed strong direct reactions, and the erythrocyte fragility test was normal. The erythrocyte count fell to 3,200,000 per c.mm. and there was a persistent leukocytosis which reached a peak of 26,000 per c.mm. Repeated urinalyses revealed no significant change from the admission specimen and the blood urea nitrogen never rose. A pleural friction rub and signs of partial consolidation appeared over the left upper lobe. The patient continued to have bloody sputum from which *S. suispestifer* was recovered on culture. On numerous occasions an early blowing diastolic murmur was heard in the third left interspace but this was by no means constant. During the last 2 weeks a pericardial friction rub was noted intermittently and for the same period of time the spleen was readily felt. Petechiæ of the skin and conjunctivæ were first noted 1 week before death. Blood cultures were positive for *S. suispestifer* on the 2nd, 7th, 8th, 9th, 13th, 15th, and 20th hospital days; one culture was negative on the 6th day. Despite the increasing icterus and decreasing erythrocyte count, large doses of sulphanilamide were started 11 days after entry and continued for 9 days without apparent beneficial effect. During this period the blood sulphanilamide concentrations as determined by the method of Marshall¹⁰ were 17, 11, 10, and 16 mg. %. The patient died on the 21st hospital day.

The clinical diagnoses were: septicemia due to *S. suispestifer* with probable acute bacterial endocarditis of pulmonary valve, rheumatic heart disease with mitral stenosis and insufficiency, auricular fibrillation, thrombosis of left subclavian and jugular veins, multiple pulmonary infarcts, and toxic hepatitis.

Necropsy (16 hours postmortem, Dr. Ritterhoff). The pericardial cavity contained 150 cc. of dark amber fluid and the visceral and parietal surfaces of the pericardium were thickened and opaque. Over the anterior surface of the right atrium there was a yellow fibrinous area approximately 3 cm. in diameter. The heart weighed 335 gm. and all its chambers were dilated. The right ventricular wall was 3 mm. thick, the left, 12 mm. The leaflets of the mitral, tricuspid, and aortic valves were thickened and opaque. The pulmonary valve presented no abnormalities. On the auricular surface of the posterior mitral cusp there was a dark, reddish-brown, firmly adherent vegetation approximately 1 cm. in diameter. Microscopic examination of the vegetation revealed an acute inflammatory reaction composed chiefly of neutrophils enmeshed in irregular masses of fibrin. Numerous Gram-negative bacilli were present. The chordæ tendineæ of the mitral and tricuspid valves were thickened, shortened, and yellowish-white in color. The mural endocardium of the right auricular appendage contained a yellowish-red firmly adherent thrombus. The upper lobes of both lungs were consolidated throughout and several dark-red, well demarcated areas

of infarction were seen in the left. The spleen weighed 225 gm., and at the superior pole there was an infarct. The kidneys together weighed 250 gm.; the left contained several areas of infarction. The liver weighed 1565 gm., the biliary passages were patent, and the parenchyma exhibited evidence of marked passive congestion. The left subclavian and jugular veins were occluded by dark red, granular thrombi.

Anatomic Diagnoses. Chronic rheumatic pancarditis with focal epicarditis, perivascular myocardial fibrosis, fibrosis of the aortic, mitral, and tricuspid valves; right auricular thrombosis; acute ulcerative mitral endocarditis; multiple infarcts of the spleen, kidneys, and lungs with associated acute fibrino-purulent pleuritis; acute splenitis; thrombosis of the left jugular and subclavian veins; subacute cholecystitis; subacute intrahepatic pericholangitis; marked chronic passive congestion and central zone necrosis of the liver.

Discussion. The organisms isolated by blood cultures in each case and from the vegetation in Case 1 gave the characteristic biologic reactions of *S. suispestifer*. The organisms failed to produce hydrogen sulphide on lead acetate media and were agglutinated in high dilution (1 to 1280) by an antiserum of the specific phase of the American type. The repeatedly positive cultures, coupled with the demonstration of many Gram-negative bacilli in sections of each vegetation at necropsy, constitute proof which seems adequate to establish this organism as the etiologic agent of the endocarditis. The etiologic significance of the organisms recovered from the blood stream of Case 2 is further suggested by the fact that they were agglutinated in a dilution of 1 to 160 by the patient's serum with the titer rising to 1 to 2560 during the period of hospitalization.

The clinical picture presented by these patients was that of a severe infectious process with endocarditis. As in most cases of *S. suispestifer* septicemia, no portal of entry for the infection was discovered and there was no known exposure to infected human beings or hogs. Petechiæ were never present in Case 1 and developed late in the course of the disease in Case 2. Clubbing of the fingers was not present in either case and peripheral embolic phenomena were absent. Each patient went downhill rapidly after entry to the hospital. The treatment was chiefly supportive. In Case 2, however, sufficient amounts of sulphanilamide were given to maintain the blood concentration between 10 and 17 mg. % for a period of 8 days. During this time the blood cultures remained positive and there was no symptomatic improvement.

It is worthy of note that although an absence of leukocytosis has been emphasized as an important finding in uncomplicated cases of *S. suispestifer* septicemia,^{5,7} both of the cases here reported had a marked leukocytosis. The appearance of leukocytosis during the course of septicemia with this organism may be of some value in the diagnosis of endocarditis, providing there is no evidence of other localization of the infection.

It is a well known clinical observation that cardiac arrhythmias are rarely associated with bacterial endocarditis of either the acute

or subacute type. Segal¹² recently reviewed the literature on this subject and in a total of 202 cases of acute bacterial endocarditis found 5 instances of auricular fibrillation, an incidence of 2.5%. That complete heart block is an even rarer occurrence is illustrated by the fact that in Segal's own series of 84 cases of acute bacterial endocarditis not a single instance was found. Each of the cases here presented had a marked disturbance of cardiac rhythm. Case 2 exhibited auricular fibrillation for the entire 3-week period of hospitalization. Case 1 had complete heart block on entry but 4 days later the rhythm had changed to partial heart block with a *P-R* interval of 0.40 second. In this case the inflammatory lesion extended through the membranous portion of the septum ("undefended space"), thus invading the region of the bundle of His before its division.

Both hearts described in this report showed distinct evidence of antecedent injury. In one instance, the vegetation was implanted on a valve scarred by a rheumatic process, a common association. In the other, the aorta and aortic valve were deformed by syphilis, yet the bacterial infection became localized on the mural endocardium overlying the "undefended space."

Summary. 1. Two fatal cases of bacterial endocarditis due to *S. suispestifer* of the American type are reported with autopsy findings. Diagnosis was established by repeated blood cultures and the findings of Gram-negative bacilli in the vegetations histologically; in one instance culture of the vegetation confirmed the presence of the causative agent.

2. The clinical course of 2 cases of endocarditis due to *S. suispestifer* was not characterized by any unusual symptoms or signs with the exception of marked cardiac arrhythmia. In one instance, auricular fibrillation occurred. In the other, complete heart block changing to partial heart block was present.

3. Sulphanilamide in large doses was given to one patient without apparent beneficial effect.

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THE USE OF ELECTROCARDIOGRAPHIC CHANGES CAUSED BY INDUCED ANOXEMIA AS A TEST FOR CORONARY INSUFFICIENCY.*†

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THAT lack of an adequate supply of oxygen to the heart will result in changes in the form of the electrocardiogram in man, was first pointed out by Greene and Gilbert in 1921.⁴ Their studies, and a number which followed, employed the rebreathing of air to bring about gradually progressive anoxemia.^{5,12} Other workers, notably Larsen of Copenhagen, permitted the subjects to inhale mixtures of constant, low oxygen concentration.⁷ Alterations in the electrocardiogram have also been studied after exercise.^{2,10,13,15} Following such procedures, slight changes have been observed in the records of normal persons. It has been inferred that more marked variations in the level of the *RS-T* junctions and in the form of the *T* waves indicate impairment of the coronary circulation. The occurrence of similar changes in graphic records taken during spontaneous attacks of anginal pain has been regarded as evidence that such pain is caused by myocardial anoxemia.^{3,11}

There can be no question as to the usefulness of an objective test which makes it possible, even qualitatively, to detect coronary insufficiency. Cardiac pain, induced either by exercise or by oxygen want, has proved to be an unreliable index, partly because it represents a subjective end-point, and also because so many complex factors are concerned in its production.⁸ Besides, many patients with disease of the coronary arteries do not experience pain. The chief difficulty in interpreting the significance of changes in the electrocardiogram caused by induced anoxemia has been due to the fact that these occur, in varying degree, in many persons without evidence of cardiac or other disease. The borderline between normal variation and pathologic response has not been established

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by measurement; nor has the precordial lead been employed in any of the previous investigations. In this study, an attempt has been made to define quantitatively the limits of normal variation and to explore the possibilities of the method with respect to its clinical applicability. The work has already been briefly recorded.⁹

Technique. The *apparatus* has been described in a previous paper⁸ (Fig. 1). A tank containing 10% oxygen and 90% nitrogen furnished an unvarying concentration of oxygen in the inspired air. The oxygen mixture was admitted at a rate comparable to the normal pulmonary ventilation. The bag was kept full but not distended. By the use of 2 flutter valves the mixture was inhaled during inspiration and exhaled during expiration, without rebreathing. A two-way valve at the mouthpiece enabled the observer to connect the patient to the apparatus while breathing room air and thus accurately to record the time that he was exposed to inhalation of a low oxygen mixture. A tank containing 100% oxygen was also in the circuit, so that if necessary, by turning a needle valve, anoxemia could be quickly relieved. At the end of each period of observation, the patient was permitted to breathe pure oxygen long enough to abolish cyanosis, or to relieve pain, if this occurred.

The *procedure* differed from that followed in a study of cardiac pain⁸ in that the gas mixture contained 10 instead of 12% oxygen; and attention was focussed on changes occurring in the form of the electrocardiogram. A 10% oxygen mixture was used because anoxemia was induced more quickly and the changes in the electrocardiograms were more sharply defined than with 12%. There was apparently no added discomfort or hazard to the patient. Observations were made at least 2 hours after the last meal. The temperature of the room in which the test was made was kept reasonably constant at about 68° F. The patient was allowed to rest in bed for a period varying from 20 minutes to 1 hour. The procedure was explained and the patient was told that as soon as he experienced pain in the chest or arms, he should raise his hand. The mouthpiece of the gas apparatus was then inserted and the nose clamp adjusted. The patient was allowed to breathe ordinary air through the valve of the apparatus for a few minutes. The test was then started by turning the control valve, the subject being unaware of the time when this maneuver was made. The usual period of observation was 20 minutes. However, if pain was experienced the low oxygen mixture was immediately shut off and 100% oxygen was administered.

A control 4-lead electrocardiogram was made, with the apparatus in place, before beginning the test and additional curves were taken at the end of 5, 10, 15 and 20 minutes, as well as after 100% oxygen had been given for approximately 1 minute, or until cyanosis was abolished. The precordial lead employed was the one designated as IVF, according to the terminology recommended by the American Heart Association.¹ In each lead measurements were made of the level of the *RS-T* junction; *T* wave; *P-R* interval; *QRS* interval; voltage of *QRS*; and rate. These were charted on individual sheets for each test made.

Material. One hundred and twelve tests were made on 105 persons. The groups studied are shown in Table 1. The 66 normals did not have symptoms or signs of cardiac or other disease. In doubtful cases, in addition to physical examination, teleroentgenograms were made of the heart and blood counts were taken to rule out the presence of anemia. The diagnosis of coronary heart disease, in the 17 cases so designated, was based on a history of anginal pain or changes in the form of the electrocardiogram,

or both.* In the 11 cases classified as "suspected but doubtful," only pain in the chest was present. The 6 patients with previous coronary occlusion, evidenced by history, clinical course and electrocardiographic records, were relatively young (average age, 47 years). They were free from symptoms at the time the test was made. In 3 of these cases, the control electrocardiogram was normal; in 3, the *T* wave was negative in Leads I, II or IVF, or in combinations of these leads. The 5 patients with anemia showed hemoglobin values ranging from 28 to 65%; the number of red cells varied from 1,600,000 to 4,100,000 per c.mm.

TABLE 1.—GROUPS TESTED (105 INDIVIDUALS; 112 TESTS).

Normal Controls—66

A. Medical students (aged 20 to 33 years. Average—24 yrs.)	45
B. Miscellaneous group (aged 21 to 68 yrs. Average—42 yrs.)	21

Coronary Heart Disease—34

A. With anginal pain	17
B. Suspected but doubtful	11
C. Old coronary occlusion (diagnosis based on clinical course and previous EKG records), with normal response to test	6

Anemia—5

Aplastic	1
Sickle cell	1
With hepatic cirrhosis	1
Hypochromic	1
Pernicious	1

Results. Significant changes occurred only in the level of the *RS-T* junctions and in the form of the *T* waves. There was no alteration in the *P-R* intervals greater than 0.02 second. The duration of *QRS* remained constant throughout. No arrhythmias occurred. Ventricular premature contractions, present in the control record in several instances, disappeared with the induction of oxygen want.

There was no correlation between acceleration in rate and alterations in form. The usual range of increase was from 15 to 30 beats per minute; the maximal range was from 2 to 52 beats. In 2 cases, the *T* waves decreased appreciably in amplitude at a time when the rate actually became slower. Although there was but little variation in rate between the first and second 10-minute periods of observation, the changes in the electrocardiograms tended to become progressively more marked.

The voltage of *QRS* often became lower in one or more leads, but the change was usually less than 4 mm. There was no ratio between variation in the amplitude of *QRS* and in that of the *T* waves.

All of the subjects became distinctly cyanotic. The level of oxygen saturation of the blood was variable, as noted in our previous studies with the inhalation of 12% oxygen;⁸ but there was no direct relationship between the degree of anoxemia and the magnitude of the changes seen in the electrocardiograms. Nor did the duration of the test determine the extent of such changes. For example,

* As yet, the opportunity has not presented itself to correlate the results of the test with anatomic lesions as found at necropsy.

in certain patients complaining of pain at the end of 4 minutes, the changes, at this time, were striking. Although alterations in the records appeared quickly, they tended to regress gradually. Even after 100% oxygen had been breathed for a minute, the return to the form of the control record was usually incomplete. It seems probable that anoxemia initiates a chemical reaction in the tissues of the heart and that metabolites, which are produced locally, accumulate. There is evidence that such substances are responsible for changes in the *RS-T* segments and *T* waves in experimental cardiac asphyxia and anoxemia.⁶ Whether the electrocardiogram reverts to its original contour more rapidly when the coronary circulation is intact than when it is impaired, is at present being investigated.

No serious untoward effects were observed. Unpleasant reactions occurred on 2 occasions. In a woman, aged 60, with symptoms of early cardiac insufficiency, the test was performed twice within an hour. Mild pulmonary edema occurred after the second period of anoxemia. An injection of morphine, with rest in the overnight ward, made her comfortable and she left the hospital the following morning. A second patient, a man, 56, gave a history of dyspnea as well as pain, and his electrocardiogram showed bundle branch block. After breathing 10% oxygen for 7 minutes, he developed non-productive cough, scattered râles in the lungs, and slight sub-sternal pain. Prompt relief was afforded by the inhalation of 100% oxygen. Because of these experiences, it was decided that the test should not be performed in the presence of cardiac insufficiency; and that it should not be given to the same patient more than once within 24 hours.

Symptoms noted in normal persons were headache, a sense of heaviness in the chest, visual hallucinations and transient dizziness—each in 1 case. In 2 patients with probable cerebral arteriosclerosis, there was transitory mental confusion. Not all of those with coronary sclerosis who gave a history of anginal attacks experienced discomfort during the test. In this respect the electrocardiogram was a more delicate index of a diminished coronary reserve than was sensitiveness to cardiac pain.

On the basis of detailed measurements made of some 700 electrocardiograms, taken during 112 tests, the following tentative criteria for normal and abnormal responses have been evolved:

Normal. 1. The *RS-T* junction is not displaced more than 1 mm. in any lead.

2. The *T* waves tend to decrease in amplitude.

3. Partial or complete reversal of the direction of *T* in Lead I or Lead IVF, or both, in the absence of any *RS-T* displacement in these leads, is of uncertain significance. It was observed in 2 of 66 supposedly normal persons.

4. Partial or complete reversal of the direction of *T* in Lead II or Lead III, or both, even though associated with *RS-T* displacement

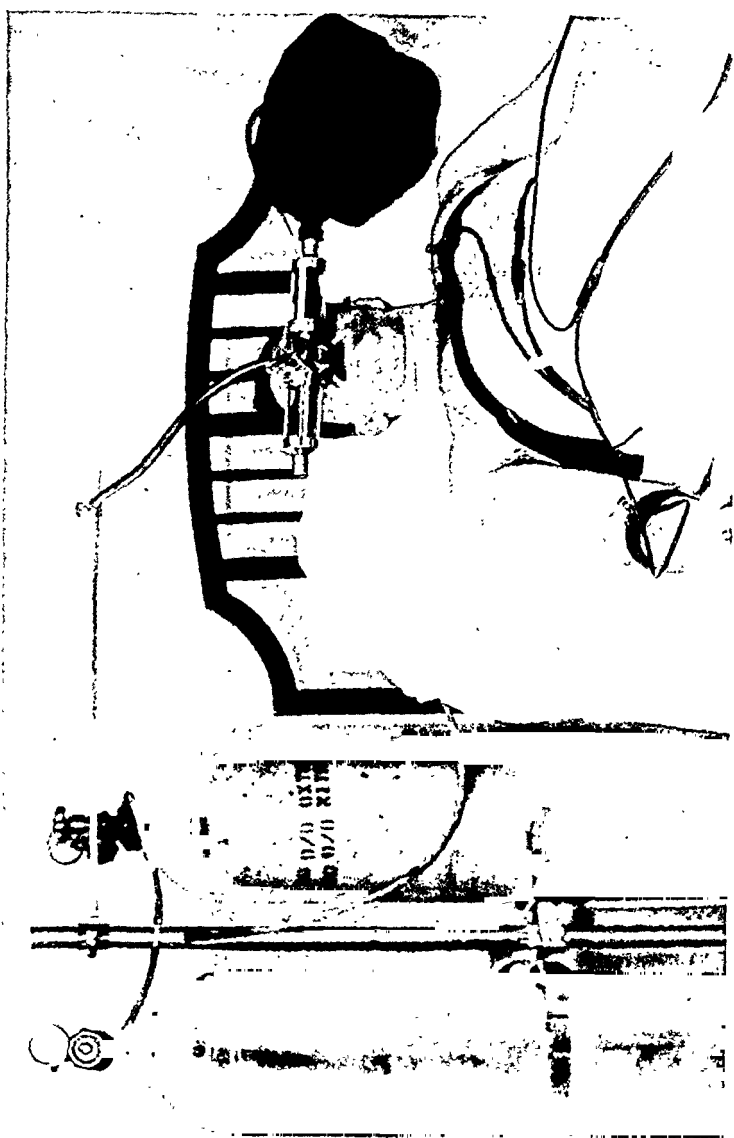


FIG. 1.—Apparatus in use.

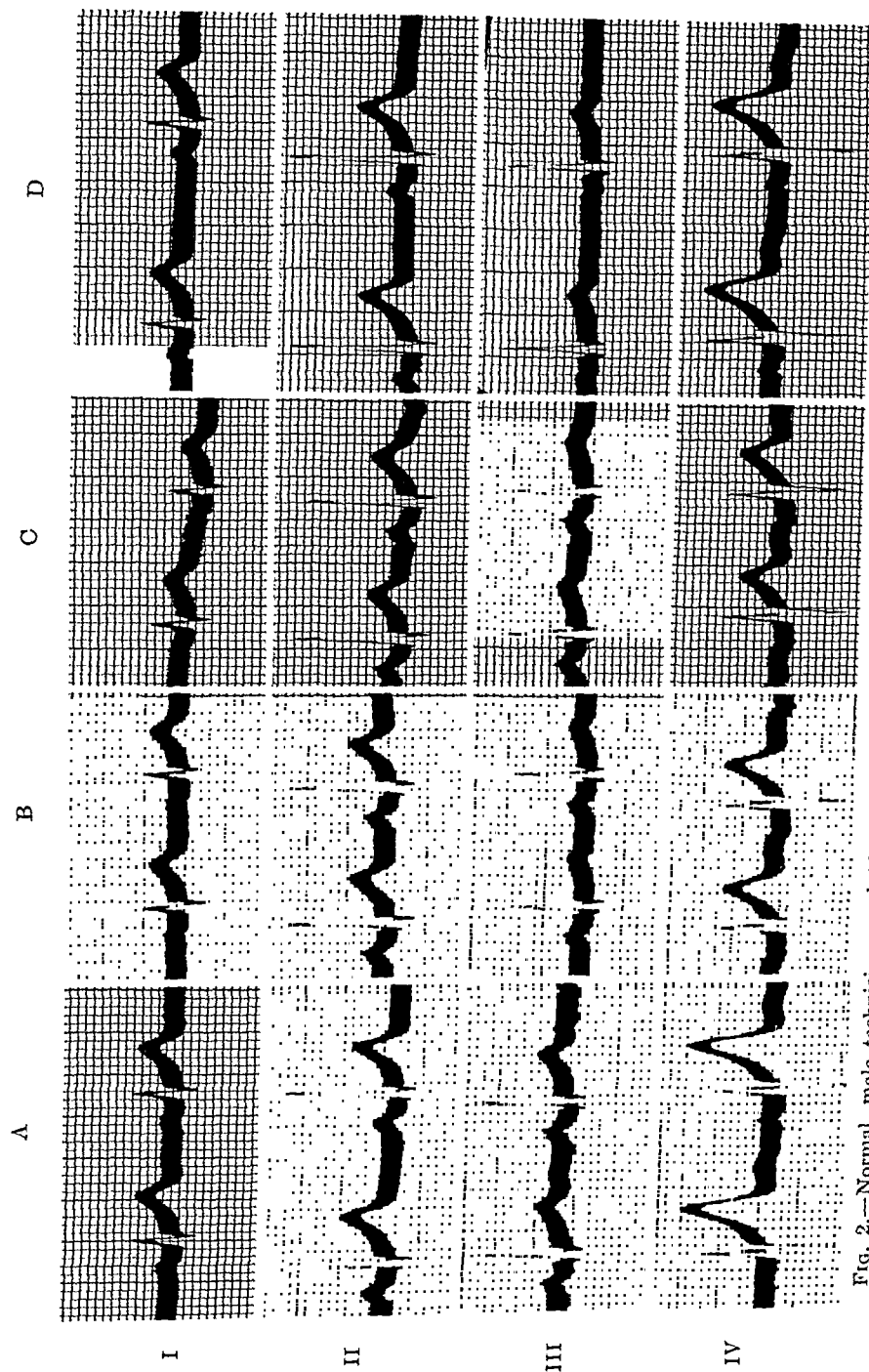


FIG. 2.—Normal, male technician, aged 20 years. *A*, control. *B*, after breathing 10% oxygen for 10 minutes. *C*, after 20 minutes. *D*, after 1 minute of 100% oxygen. In *B* and *C*, the amplitude of *T* was slightly diminished. In *D*, there was almost complete return to the form of the control.

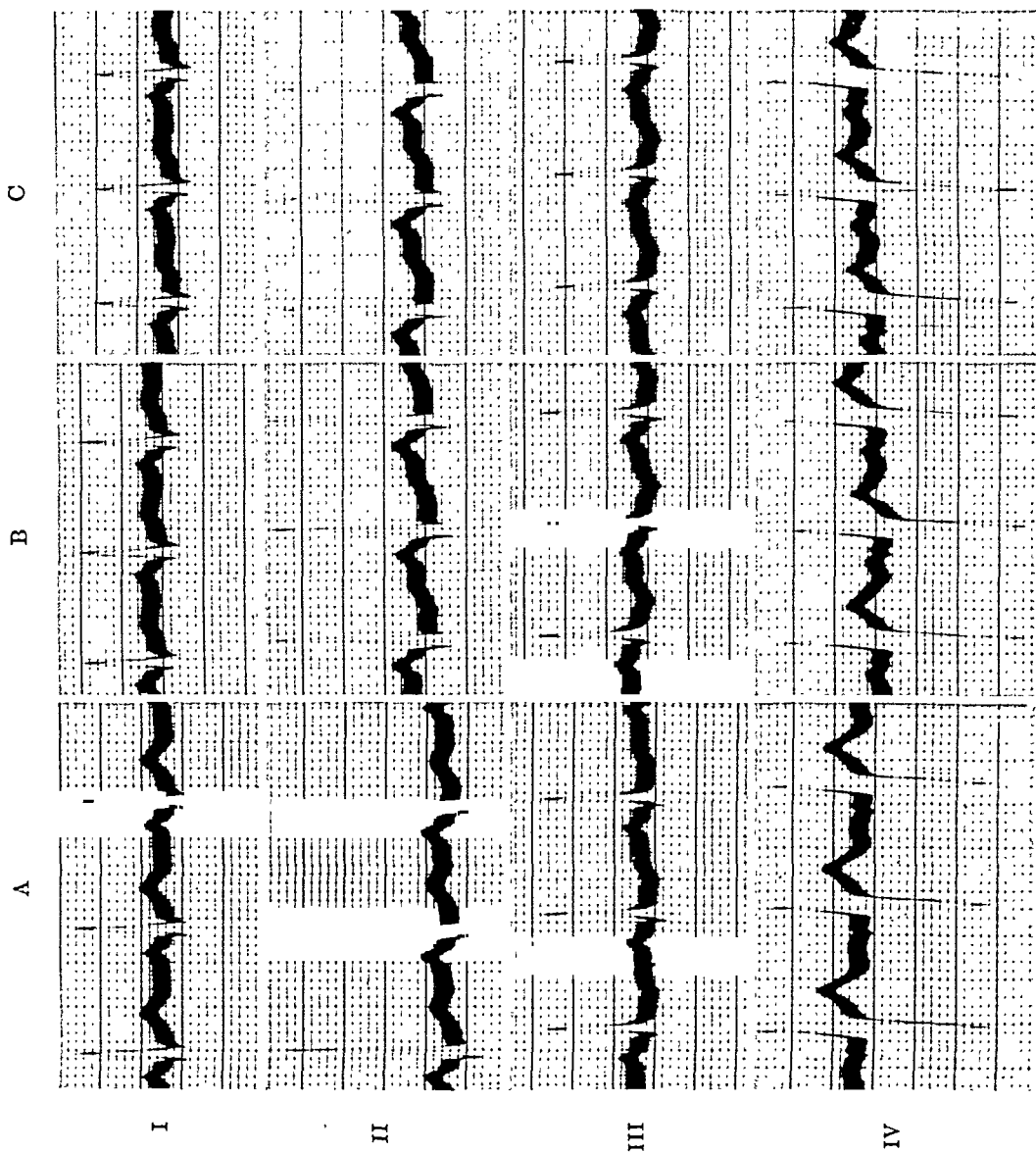


FIG. 3.—Normal, male medical student, aged 25 years. *A*, control. *B*, after 10 minutes of 10% oxygen. *C*, after 20 minutes. T_1 and T_2 became progressively lower, T_2 reversed its direction.

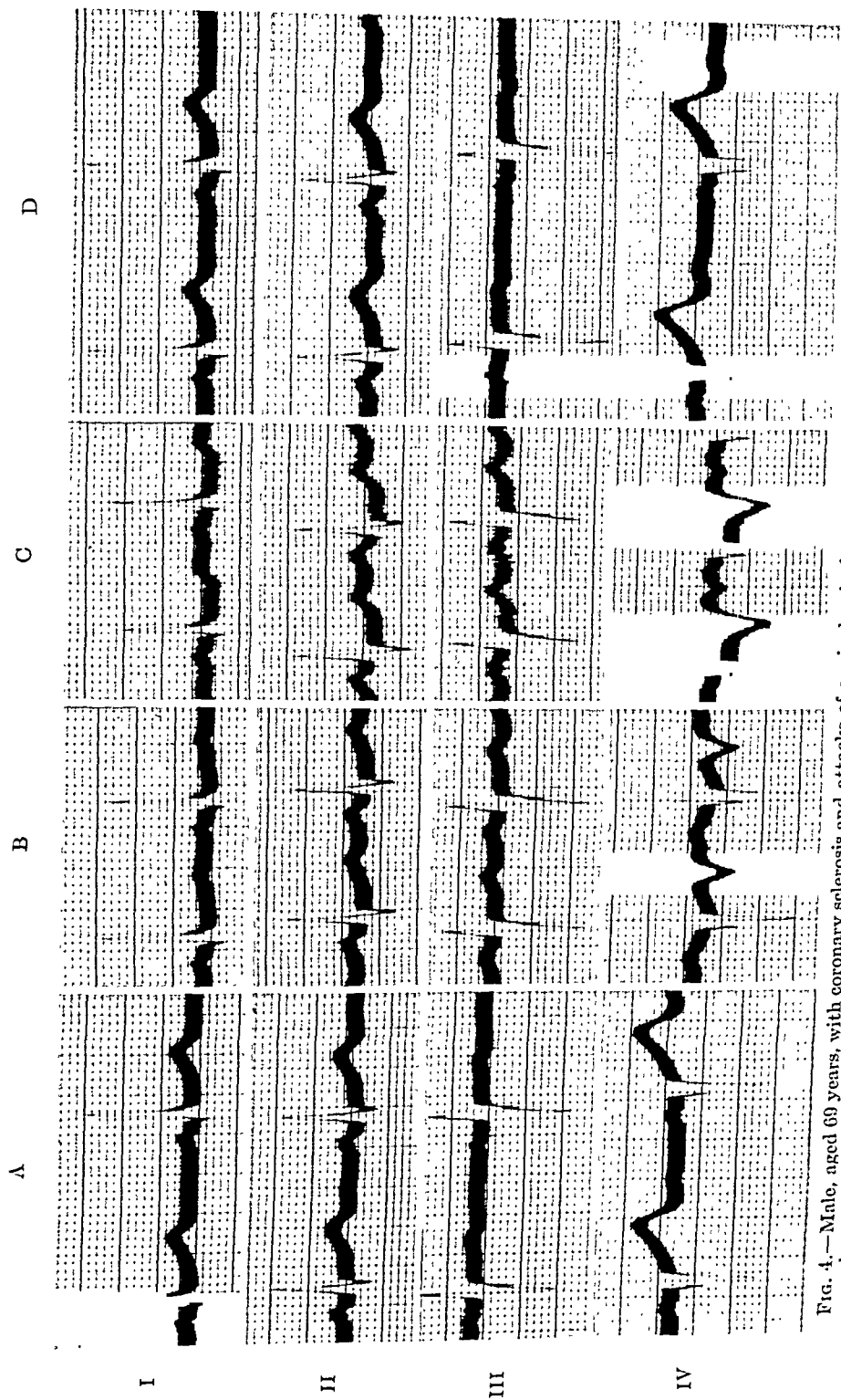


FIG. 4.—Male, aged 69 years, with coronary sclerosis and attacks of anginal pain for 5 years. Physical examination negative. A, control; a normal record. B, after 5 minutes of 10% oxygen. C, after 8 minutes; complained of pain; test stopped. D, after 1 minute of 100% oxygen. T₁ and T₂ reversed their direction. RS-T junction depressed in all leads. In D, reversion to the form seen in A.

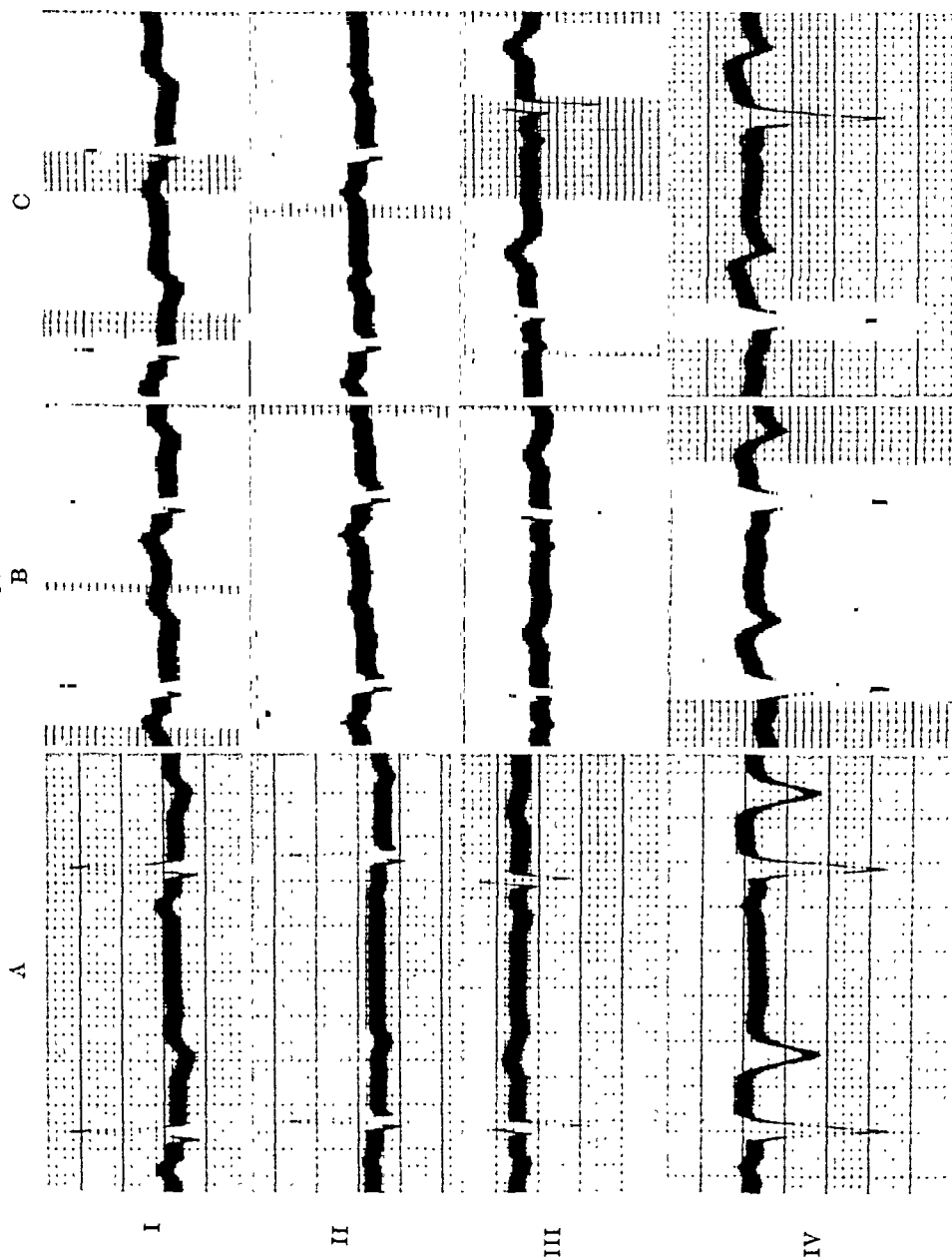


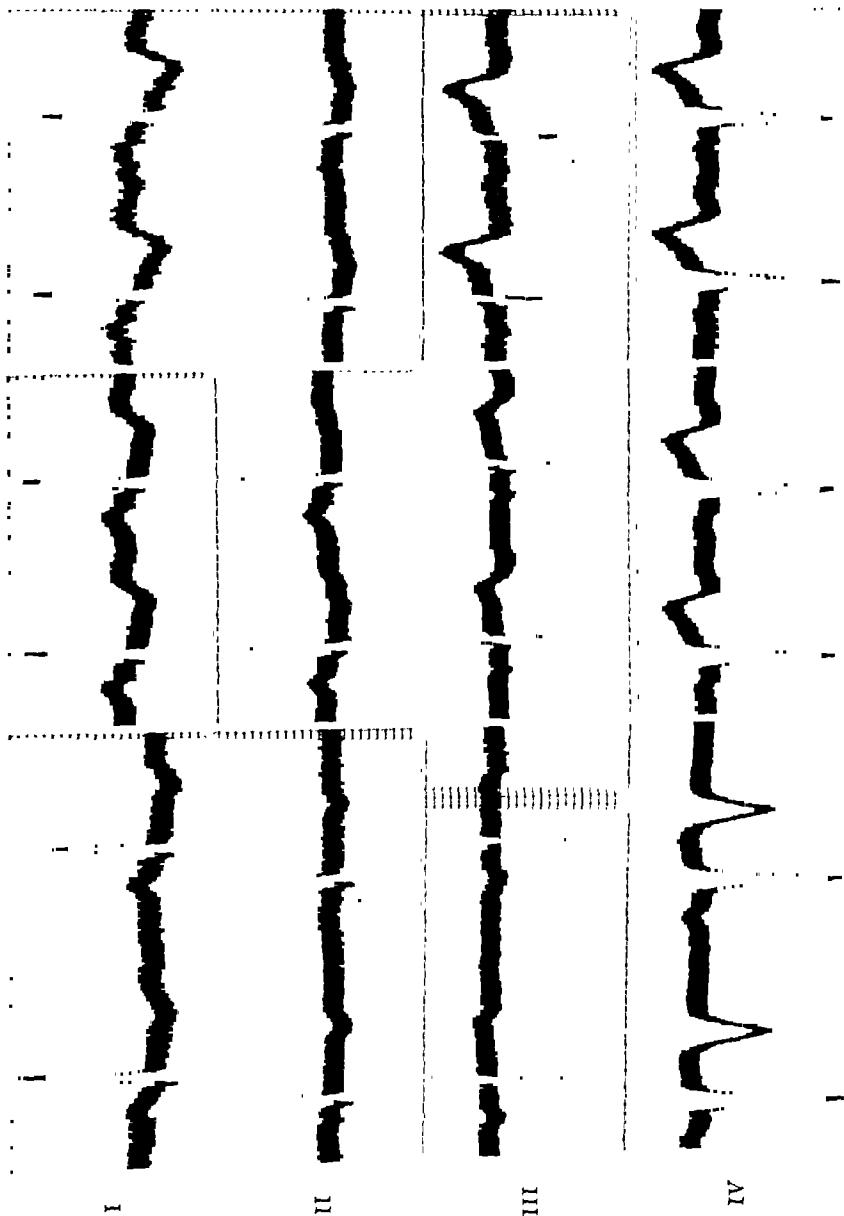
FIG. 5.—Male, aged 56 years, with coronary sclerosis. Coronary occlusion with infarction of myocardium in July, 1937. Good recovery. In December, 1937, having anginal attacks. *A*, control. *B*, after breathing 10% oxygen for 10 minutes. *C*, after 20 minutes; slight pain; felt faint. Changes in *T* and *RS-T* in all leads. *T*₁ completely reversed its direction. In February, 1938, clinically much improved; no anginal attacks. *A*, control. *B*, after breathing 10% oxygen for 10 minutes. *C*, after 20 minutes. No discomfort. Changes less marked in all leads. *T*₁ only partly reversed its direction.

December, 1937

A

B

C



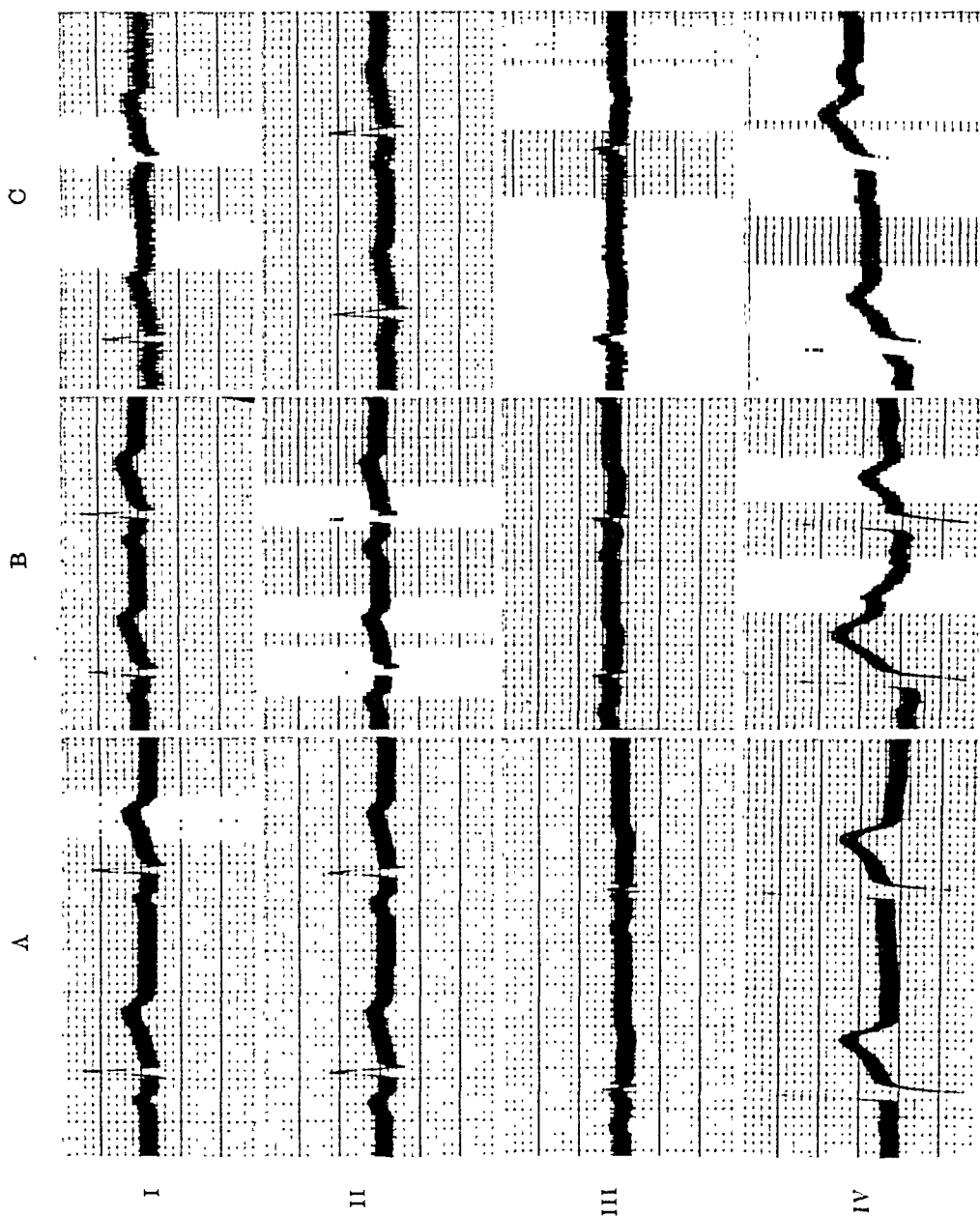


FIG. 6.—Male, aged 53 years, complaining of precordial pain for 6 years. Physical examination negative. Collecting disability insurance and suspected of malingering. *A*, control; a normal record. *B*, after breathing 10% oxygen for 5 minutes. *C*, after 10 minutes; complained of pain; test stopped. No significant changes. In *B*, Lead IV, subject moved to indicate discomfort.

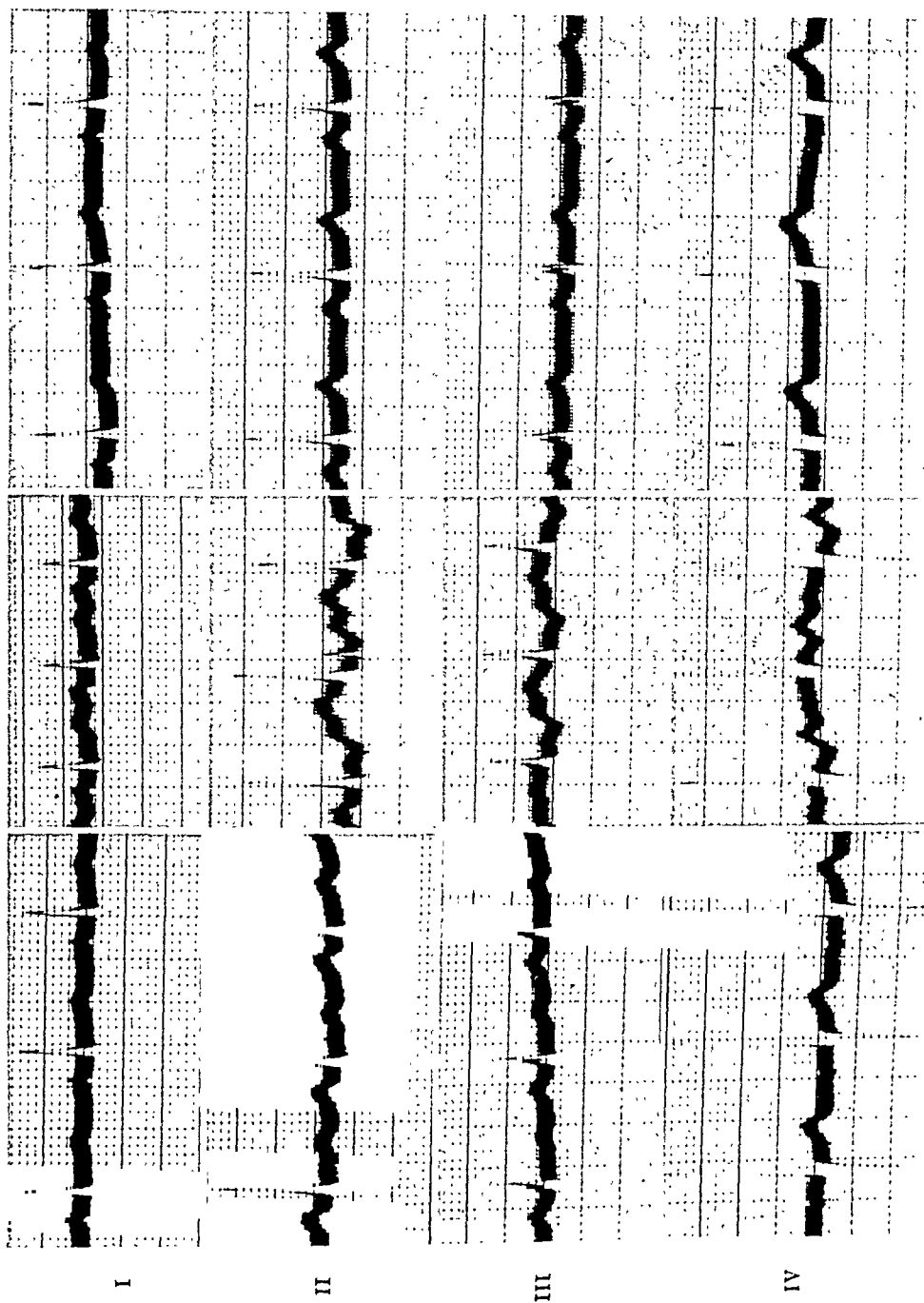


FIG. 7.—Male negro, aged 31 years, with sickle-cell anemia. No evidence of cardiac disease. Hb., 46%; R.B.C., 2,200,000. A, control. B, after breathing 10% oxygen for 20 minutes; no pain. C, after 1 minute of 100% oxygen. There are marked changes in Leads II, III and IV. In C, the form of the control is resumed.

of less than 1 mm., is of no significance. It was observed in 22 of 66 supposedly normal persons.

Abnormal. 1. A change in the level of the *RS-T* junction of more than 1 mm. in any lead, even though unassociated with changes in the *T* waves, is abnormal. Its importance is increased if combined with partial or complete reversal in the direction of *T* in Leads I or IVF, or both.

2. Partial or complete reversal in the direction of *T* in Lead I is abnormal when associated with any displacement of the *RS-T* junction in this lead. Such displacement may be as little as 0.5 mm.

3. Complete reversal in the direction of *T* in Lead IVF is always abnormal.

4. Partial reversal of the direction of *T* in Lead IVF, associated with any displacement of the *RS-T* junction in this lead, is abnormal. Such *RS-T* displacement may be as little as 0.5 mm.

Comment. In several of the students in the younger control group, the test was repeated. In 3, changes noted in the first series of records were not observed in the second, or were of lesser degree. In the older control group, the alterations, in general, were not as marked and there was less tendency for variations in repeated tests. The reason for this difference in response is not now apparent (Figs. 2 and 3).

None of the normal persons and none of those with anemia experienced pain during anoxemia. Of 17 with coronary sclerosis and spontaneous attacks of pain, all showed abnormal electrocardiographic responses to the tests (Fig. 4). Twelve complained of pain after varying periods. They were immediately given 100% oxygen, with prompt relief. One patient had suffered an attack of coronary thrombosis 6 months previously. He was having anginal paroxysms on effort and complained of pain during the first test; but 3 months later, when much improved and free from spontaneous pain, he was able to breathe 10% oxygen for the full 20 minutes without discomfort. The difference in the degree of change in the electrocardiograms in tests made at these times portrays graphically the improvement in the coronary circulation (Fig. 5).

In 11 patients with suspected but doubtful coronary disease, the test was negative and confirmed the clinical impression that discomfort was not of cardiac origin. One man, who gave a good description of anginal pain, and who had been collecting disability insurance for 6 years, was suspected of malingering (Fig. 6). Because of the support lent by the test to the examining physician's opinion, it was recommended that disability payments be discontinued.

In 6 patients with previous coronary occlusion and healed myocardial infarcts, the test yielded negative results. One complained of pain and one of mild substernal pressure during the period of anoxemia. The absence of changes in the form of the electrocardio-

grams, in view of the fact that these patients were clinically well, may be regarded as indicating that the remaining coronary arteries were able to maintain an adequate flow of blood through the heart muscle. The "coronary reserve" was apparently sufficient to meet the added demands imposed by oxygen want.*

In 5 patients with marked anemia but without signs of cardiac disease, significant changes in the *T* waves occurred in every instance, comparable to those seen in the presence of coronary sclerosis (Fig. 7). Anoxemia added to severe anemia brought about the same result, in this respect, as when added to ischemia; but pain was conspicuously absent. It is also noteworthy that in no case were the *RS-T* junctions displaced more than 1 mm.

Summary. 1. A method has been described for inducing generalized anoxemia without rebreathing, employing an apparatus which enables the subject to breathe a mixture of 10% oxygen and 90% nitrogen at the normal rate of pulmonary ventilation.

2. Changes in the form of the electrocardiogram have been analyzed following the induction of anoxemia in 105 persons, comprising 66 normals, 23 with disease of the coronary arteries, 11 in whom coronary disease was suspected but doubtful, and 5 with severe anemia.

3. Criteria for normal and abnormal responses have been evolved. It is recognized that the material is relatively small and that the criteria must be regarded as tentative. It has not been possible, thus far, to correlate the clinical diagnoses with the anatomic lesions.

4. Changes regarded as abnormal have occurred in patients with clinical symptoms and signs of coronary insufficiency. Similar alterations have been observed in those with anemia but without signs of cardiac disease.

5. There have been no serious untoward effects. Because of two unpleasant reactions, it is suggested that the test should not be given to patients with cardiac insufficiency and should not be repeated in the same patient within 24 hours.

6. Changes in the form of the electrocardiogram caused by induced anoxemia may be used as a clinical test for insufficiency of the coronary circulation, whether this be manifest or latent. An index is afforded of the adequacy of the "coronary reserve." It should be of value in distinguishing pain of coronary origin from pain in the chest due to other causes, as well as from pain referred from the

* In this connection, the comments of Dr. Charles C. Wolferth, of Philadelphia, are of interest. He discussed our paper when it was first presented,² and in a recent letter wrote as follows: "One of the striking features of infarction of the lateral or postero-lateral part of the left ventricle is the fact that the electrocardiographic changes appear to be quite transient and after the *RS-T* interval deviations have disappeared there may remain no evidence of myocardial damage, even though later necropsy may reveal the presence of a large infarct. It was this observation that made me raise the point I did in the discussion of your paper. I am inclined to think, therefore, that the presence or absence of change may not depend entirely on the state of the collateral circulation in lesions involving this part of the heart."¹⁴

abdomen. It is possible that it can be employed also to study, in man, the effect of drugs and of various surgical procedures on the efficiency of the coronary blood flow. Such studies are in progress.

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SEROLOGIC AND IMMUNOLOGIC STUDIES RELATIVE TO THE VIRUSES OF HUMAN AND SWINE INFLUENZA.*

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DURING the studies of epidemic influenza previously reported³ it became important to determine whether the virus strains used in the tissue culture vaccine during the winter of 1936-37 were related immunologically to the virus strain subsequently recovered by ferret and mouse passage from cases of epidemic influenza during the same winter and in the same State Colonies. The present report records such immunologic studies.

Also following the epidemic influenza of 1936-37, Shope,² while examining sera from swine suffering from hog cholera in another State Colony, noted the presence in the sera of neutralizing properties against the human influenza virus (PR-8) and the absence in the same sera of such antibodies against the swine influenza virus. (Epidemic influenza had apparently occurred at this Colony, although no nasopharyngeal washings of the inmates were studied.

* Assisted by a grant from the Bureau of Animal Industry, U. S. Department of Agriculture, The Lyophile Serum Fund of the Abington Memorial Hospital, and the International Health Division of the Rockefeller Foundation.

It was particularly significant that the sera of young pigs taken subsequent to the epidemic of influenza showed no neutralizing properties against either virus. Human influenza viruses Phila 37-9 and Phila 37-7 had been obtained from Colonies J. and M. L., respectively,³ in 1937, the former having been furnished Shope for studies on the sera of swine from this same colony, J.)

In addition to these observations recorded,² it appeared desirable to extend the serologic studies over a larger group of viruses, including Phila 37-7, recovered from Colony N. L. There are included, therefore, in the present report studies of the neutralizing properties of the swine sera obtained from the swine in the Colonies against the swine influenza virus (S-15) and against several of the important human influenza virus strains mentioned, including the W.S. (English) strain.

Results of Studies With Human Influenza Virus Used in Tissue Culture Vaccine. *Cross-immunity Tests.* The experience with the strains of human influenza virus Phila 37-7, Phila 37-9 and Phila 37-1 isolated during 1937 in Colonies J. and N. L., and in Philadelphia respectively by ferret and mouse passage from nasopharyngeal washings of ill patients was in agreement with that recorded by Andrewes, Smith and Harris,⁴ in the study of a larger number of strains isolated during the same year in England. Not only was it possible to produce cross-immunity in ferrets and mice with these strains isolated in 1937, but a cross-immunity could be produced with all of these strains against the PR-8 virus, the original strain used in the tissue culture vaccine.³ Since slight antigenic differences, not greatly affecting cross-immunity in animals, have been shown to exist,^{1,4} a number of strains* of human influenza virus were used for all vaccine injections in the colonies during the winter of 1937-38.

Cross-neutralization Tests. In Tables 1 and 2 are recorded samples of cross-neutralization tests with sera of ferrets recovered from infection with human influenza virus strains Phila 37-9 and Phila 37-7. These tests showed no cross-neutralizing properties against the swine virus whereas the opposite was true in the tests against the human viruses. There appeared to be slight differences in the rapidity of development of the neutralizing properties against the human viruses. The W.S. (English) strain was not used in all tests due to insufficient serum. Andrewes, Smith and Harris⁴ in titrating convalescent ferret sera against different strains of human influenza virus have clearly demonstrated antigenic differences which appear to separate roughly the human viruses used in their studies into three groups. Despite very marked differences found by them cross-neutralization to a greater or lesser extent did occur among all their strains. The marked differences were apparent in but 1 or 2 strains.

*The strains included PR-8, W.S., Melbourne, Phila 37-1, Phila 37-7, Phila 37-9. Phila (1935).

TABLE 1.—CROSS-NEUTRALIZATION TESTS WITH THE SERUM FROM A FERRET BEFORE INFECTION AND FOLLOWING RECOVERY FROM INFECTION WITH THE NEW LISBON STRAIN OF VIRUS.

Ferret E—4 injected intranasally on Jan. 21, 1938 with 0.5 cc. of 2% suspension of mouse lung, infected with virus Phila 37-7 (New Lisbon Strain).

Dates on which blood samples were taken:	Jan. 19.	Jan. 28.	Feb. 1.	Feb. 5.
Virus strain.				
PR-8	4 4 4*	0 0 0	0 0 0	0 0 0
Phila 37-9	4 4 4	0 0 0	0 0 0	0 0 0
Phila 37-7	4 4 4	0 0 0	0 0 0	0 0 0
S-15	N.S.Q.†	4 4 4	4 4 4	N.S.Q.†
W.S.	4 1 1

* The figures represent the degree of lung involvement of the mice as usually expressed in neutralization tests, i. e., 4 represents complete consolidation of the lungs, while 2 represents consolidation of approximately one-half of the lungs.

† Not a sufficient quantity of serum obtained for testing.

TABLE 2.—CROSS-NEUTRALIZATION TESTS WITH THE SERUM FROM A FERRET BEFORE INFECTION AND FOLLOWING RECOVERY FROM INFECTION WITH THE JAMESBURG STRAIN OF VIRUS.

Ferret E—5 injected intranasally on Jan. 21, 1938 with 0.5 cc. of 2% suspension of mouse lung, infected with virus Phila 37-9 (Jamesburg Strain).

Mouse Lung Involvement.

Dates on which blood samples were taken:	Jan. 19.	Jan. 28.	Feb. 1.	Feb. 5.
Virus strain.				
PR-8	4 4 4*	2 2 2	0 0 0	0 0 0
Phila 37-9	4 4 4	1 1 1	1 0 0	0 0 0
Phila 37-7	4 4 4	1 1 1	0 0 0	0 0 0
S-15	4 4 4	4 4 4	4 4 4	4 4 4
W.S.	0 0 0

* The figures represent the degree of lung involvement of the mice as usually expressed in neutralization tests, i. e., 4 represents complete consolidation of the lungs, while 2 represents consolidation of approximately one-half of the lungs.

From these results it is evident that the viruses used in the chick embryo tissue culture vaccine had a close antigenic relationship to the viruses recovered in the State Colonies, one-third of whose inmates had received the vaccine. This would appear to strengthen the evidence obtained suggesting the value of such vaccine as an immunizing agent against epidemic influenza.³

Results of Cross-neutralization Tests on Swine Sera. *Sera.* The samples of swine sera were kindly sent us by Dr. R. E. Shope, who had obtained them from swine on the Bordentown State Prison Farm and on the farm of the Jamesburg Reform School. The swine sera marked "young pigs" were from animals born and bled after the 1937 influenza epidemic and the swine sera marked "old pigs" were from animals born before the 1937 influenza epidemic and bled after the epidemic. The herds of swine and their contacts with the inmates of the colonies has been previously mentioned.²

Viruses. The virus strains employed in the neutralization tests were the human influenza virus strains PR-8 (Francis); English W.S. (Wilson Smith); Phila 37-9 (Jamesburg); Phila 37-7 (New Lisbon); and the swine influenza virus strain S 15 (Shope).

All virus suspensions used in the tests were 2% suspensions of infected mouse lung with the above respective strains except for Phila 37-7 which was a 5% suspension. The sera and virus suspension were added in equal proportions and incubated at 37° C. Six anesthetized Swiss mice were inoculated intranasally by means of a pipette with 0.05 cc. of the mixture.

The experiment terminated at the end of the tenth day and all surviving mice were killed and the lungs were examined for gross pulmonary lesions.

Tables 3 and 4 record the cross-neutralization tests against the strains of influenza virus mentioned. They are not strictly comparable to the tests recorded by Shope, since in these present studies 6 mice were used for each cross-neutralization test and the surviving mice were not killed until the tenth day. In general, however, the tests are quite comparable and although a larger number of virus strains were used in the present studies, nevertheless among the tests of those strains used in both studies there was satisfactory agreement. At Colony B all sera obtained from pigs born after July, 1937, showed no neutralizing properties against any strain of human or swine influenza virus, whereas most of the sera obtained from pigs born before November, 1936, showed marked neutralizing properties against all of the human virus strains used, although none against the swine strain. A few exceptions may be noted such as Nos. 15, 20 and 21 which suggest the existence of slight antigenic differences between the human virus strains. There was an insufficient amount of serum in the case of No. 15 to make a test against the swine virus.

The antigenic differences among the human strains appeared more significant in the cross-neutralization tests on the sera from the herd of swine attached to Colony J, from which virus strain Phila 37-9 was obtained. For example, in Figs 4, 9, 12, 13 and 14 the differences are very striking in the neutralization tests against the two viruses, Phila 37-9 and Phila 37-7. Since virus Phila 37-7 had never been as virulent in mice as Phila 37-9 a 5% suspension of Phila 37-7 had been used as mentioned rather than the 2% suspension used for Phila 37-9. This permitted a direct comparison of the neutralizing properties of the sera since all of the controls for each virus died in a comparable period (Tables 3 and 4). In Colony J, also, the sera of young pigs born after July, 1937, showed no neutralizing properties against either the swine or human virus, whereas those born before November, 1936, in most instances, showed partial or complete neutralization of the human virus strains.

It will be noted in a comparison of the results shown in Table 4 with those recorded by Shope² that serum from old Pig 7 showed no neutralizing properties against strain Phila 37-9 in the present studies, whereas repeated tests of this serum by Shope confirmed an antigenic difference between strains Phila 37-9 and PR-8. Insufficient serum from this pig was available to check further these findings in the present studies. In other respects, the two studies were in essential agreement.

Discussion. The close relationship of all strains of human influenza virus so far isolated is emphasized by the results of the present studies on cross-immunity and cross-neutralization with viruses isolated from different localities during the mild pandemic of influenza of 1936-37. A comparison with strains from previous years and from other parts of the world gives added confirmation to this

relationship. The antigenic differences in certain strains, however, should not be disregarded nor should there be overlooked the apparent lack of marked significance of these differences as far as they are related to cross-immunity. From these results it would seem worthwhile to use at least several strains of virus chosen for their antigenic differences in the development of a chick embryo tissue culture vaccine.

The cross-neutralization studies on swine sera initiated by Shope and carried on with a larger number of virus strains at the Children's Hospital also afforded the opportunity of studying antigenic differences in strains of virus isolated in this Laboratory and originally transmitted to the swine under ordinary or natural field conditions: a fact which should make the cross-neutralization tests on the sera of even greater significance.

Summary. 1. The immunologic and serologic relationships between the human influenza viruses used as a vaccine and the human influenza viruses isolated in the Colonies vaccinated during a subsequent epidemic of influenza are described.

2. The development of neutralizing antibodies against the human virus in the sera of swine exposed to human epidemic influenza and the absence in the same sera of corresponding antibodies for the swine virus are described. The appearance in the cross-neutralization tests of antigenic differences in the human influenza viruses isolated is also described and discussed.

We are indebted to the Department of Institutions and Agencies of the State of New Jersey for their interest and cooperation in these studies.

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COMPLEMENT-FIXATION STUDIES ON THE SERA OF INDIVIDUALS VACCINATED WITH ACTIVE VIRUS OF HUMAN INFLUENZA.*

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THE present report concerns studies of the complement-fixing antibodies in the sera of individuals vaccinated with the active

* These studies were assisted by grants from the Bureau of Animal Industry, United States Department of Agriculture, The Lyophile Serum Fund of the Abington Memorial Hospital, and the International Health Division of the Rockefeller Foundation.

virus of human influenza during 1937 and 1938 and in the sera of a group of controls in large State Colonies, as previously described.⁵ There are included studies of the sera of individuals suffering from respiratory infections, non-influenzal in type, during the late winter and spring of 1938.

Wilson Smith⁴ first demonstrated a complement-fixation test for the titration of influenzal antibodies in the sera of men and experimental animals, also showing a fairly close correlation between this test and the neutralization test on the same sera. Fairbrother and Hoyle^{1,3a} also described a complement-fixation test for antibodies in human sera and later^{3b} demonstrated that "the complement fixing antigen is a soluble substance probably liberated during multiplication of the virus in the tissues." This observation is of significance in relation to the production of complement-fixing antibodies as a result of vaccination. According to such findings the complement-fixing antibody response should depend upon the type of vaccine used, whether infected mouse lung or tissue culture vaccine.

Francis *et al.*² made the first extensive study of complement-fixation and neutralization tests on the same sera obtained from individuals during both the acute and convalescent stages of epidemic influenza. Parallel tests were also made by the same workers upon the sera of individuals in close contact with influenzal patients, and upon the sera of others with non-influenzal respiratory infections. In these studies the titers of both antibodies were markedly increased by acute influenzal attacks, whereas there were but slight increases in the sera of the contact cases, and no increase in the sera of those suffering from non-influenzal infections.

Since in the present studies large numbers of individuals had been vaccinated with active human influenza virus as previously reported,⁵ it was important to determine the effect of such vaccine injections upon the complement-fixing antibodies of their sera, together with a similar and simultaneous study of the sera of a group of non-vaccinated controls. It was possible also to fulfill partially a general objective of studying the sera of the same individuals over a period of 1 to 2 years under similar well-controlled environmental conditions but in the presence of a variety of intercurrent respiratory infections.

Technique of Complement-fixation Test. *Antigen.* Healthy white Swiss mice were inoculated intranasally under ether, with a 10% suspension of mouse lung infected with the PR-8 virus strain. These mice were killed when moribund, and the lungs removed aseptically and ground in a mortar with sterile powdered glass. Normal saline, 1.5 cc., was added per lung and the suspension centrifuged at 3000 r.p.m. for 30 minutes. The supernatant was filtered through a Type V Berkefeld filter and bottled in 20 cc. amounts in sterile bottles. The antigen was stored at -10° to -15° C. and the titer was found to remain fairly constant after the first week of storage and did not become anticomplementary upon standing 8 weeks at this temperature.

The antigen was titrated each time before using for hemolytic, anticomplementary and antigenic units and was then diluted so that 0.5 cc. contained 5 antigenic units.

Antigen was also prepared from virus grown on minced chick embryo in Tyrode's solution. The antigenic titer of this preparation was very low and unsatisfactory for use. Antigen prepared from tissue culture which had been preserved by drying *in vacuo* at a low temperature and regenerated to one-half its original volume gave a high antigenic titer in some instances.

Due to the factor that the vaccine, which was injected into individuals at the various State Colonies was prepared from tissue cultures of the virus strain, the better antigen for use in testing sera from vaccinated individuals was that prepared from infected mouse lungs.

Known positive sera tested against normal mouse lung antigen and tissue culture antigen with no virus gave negative results.

Complement. Fresh guinea pig sera were titrated and diluted so that 3 minimal hemolytic doses were contained in 1 cc. of diluted serum.

Sera. A pool of immune rabbit sera was used as the standard each time. The rabbits were immunized against PR-8 virus strain grown on minced chick embryo culture medium. The titer of the standard pool was 1 to 256 for complement-fixing antibodies and 1 to 320 for neutralizing antibodies.

All sera had been collected and stored under sterile conditions. The sera were kept at 3° C. until tested and then were inactivated by heating at 56° C. for 30 minutes.

The test was set up according to Table 1.

TABLE 1.—COMPLEMENT-FIXATION TEST FOR INFLUENZA.

Tube:	1	2	3	4	5	6	7	8
Serum diluted:	Undil.	1 : 4	1 : 8	1 : 16	1 : 32	1 : 64	1 : 128	Contro
	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Antigen-infected mouse lung with PR-8 virus (Berkefeld filtered 5 units in 0.5 cc.)	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	
<i>Room Temperature for 15 Minutes.</i>								
Complement, 3 units in 1 cc.	1 cc.	1	1	1	1	1	1	1
Incubate 2 hours, 37° C.—water-bath.		Overnight	3° to 6° C.—icebox.					
Antisheep amboceptor, 2 units in 0.5 cc.	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
2% sheep cells	0.5 cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Incubate 1 hour, 37° C.—water-bath.								

The results were read immediately upon taking the tubes from the water-bath and again after a sufficient time in the icebox, to allow the sedimentation of the suspended sheep cells. Final readings were made at this time, and the end point was considered as the last tube in which complete fixation occurred. As a rule, the end points were quite sharp.

Results. A study was made during the recent winter, 1937-38, when epidemic influenza was absent, of sera obtained from individuals both during the acute and convalescent stages of respiratory infections. Nose and throat washings were collected from many of these individuals but no influenza virus was obtained following ferret passage. Table 2 indicates the complement-fixing antibodies in such sera from groups of vaccinated and non-vaccinated individuals, whose febrile response and general type of respiratory infection are also recorded. These groups of individuals at Colony S represented the only epidemic of respiratory infection of any significance occurring in the State Colonies studied during this winter, 1937-38, and the incidence in the vaccinated and non-vaccinated

groups was almost identical. Whether such infections occurred in the vaccinated or non-vaccinated group there appeared to be no difference in the titer of complement-fixing antibodies. Also in comparing the sera from the acute and convalescent stages of both groups the titer was fairly constant.

TABLE 2.—SKILLMAN COLONY—VACCINATED GROUP.

Complement-fixation test on blood samples collected.					
Name.	2-8-38	2-28-38	Clinical history.		
	Complete fixation in serum dilution.		Date, hosp.	Highest temp. °C.	Diagnosis.
M. H.	1 : 16	1 : 16	2- 7-38	100.0	U. R. I.
R. H.	1 : 16	1 : 16	2- 7-38	100.2	U. R. I.
N. C.	1 : 16	1 : 16	2- 6-38	105.0	U. R. I.
P. B.	1 : 32	1 : 16	2- 8-38	101.2	Otitis media
A. D.	1 : 4	0	2- 8-38	100.4	U. R. I.
C. B.	0	0	2- 6-38	104.6	U. R. I.
C. A.	1 : 16	1 : 4	2- 8-38	101.0	U. R. I.
	2-23-38	3-14-38			
E. J.	1 : 8	1 : 4	2-21-38	98.2	U. R. I.
S. B.	1 : 8	1 : 8	2-21-38	100.6	U. R. I.
W. C.	1 : 4	0	2-20-38	103.0	U. R. I.
Non-vaccinated Group.					
	2-8-38	2-28-38			
B. W.	1 : 16	1 : 8	2- 7-38	102.0	U. R. I.
E. Y.	1 : 64	1 : 32	2- 7-38	101.4	U. R. I.
N. C.	1 : 8	1 : 8	2- 6-38	100.0	U. R. I.
E. W.	1 : 16	1 : 8	2- 5-38	100.0	U. R. I.
H. S.	1 : 32	1 : 8	2- 7-38	100.8	U. R. I.
C. M.	1 : 32	1 : 32	2- 8-38	102.0	U. R. I.
H. G.	0	0	2- 8-38	101.2	U. R. I.
S. M.	1 : 4	1 : 4	2- 8-38	105.4	Otitis media
R. H.	0	0	2- 8-38	102.2	U. R. I.
	2-23-38	3-14-38			
J. R.	0	0	2-21-38	102.2	U. R. I.
B. M.	1 : 2	0	2-21-38	101.0	U. R. I.
F. M.	1 : 8	1 : 8	2-21-38	99.2	U. R. I.
J. H.	1 : 2	0	2-21-38	100.0	U. R. I.
F. W.	1 : 4	1 : 4	2-21-38	101.0	U. R. I.
R. M.	0	0	2-21-38	100.2	U. R. I.
P. M.	1 : 2	0	2-20-38	100.2	U. R. I.
C. P.	0	0	2-22-38	101.4	U. R. I.
J. L.	1 : 16	1 : 16	2-21-38	101.0	U. R. I.
L. S.	0	0	2-21-38	101.0	U. R. I.
J. L.	1 : 4	1 : 2	2-21-38	99.6	U. R. I.

In a determination of the fluctuation of complement-fixing antibodies in the sera of hospital personnel during the seasonal height of respiratory infections, sera were obtained from physicians, nurses and social workers at the Children's Hospital during the late winter and early spring of 1938, as shown in Table 3. No significant changes for the three determinations are noted, except for a possible tendency to a decrease in titer.

Tables 4 and 5 record the titers in the sera of a vaccinated and a non-vaccinated group of individuals from Colony N.L. over a period of 2 years. The sera in both years were obtained before vaccine injections were given and again 2 weeks following the final vaccine injection. In the winter of 1936-37 the sera were obtained before the occurrence of epidemic influenza.

In Tables 6 and 7 are recorded comparisons of the titers of sera obtained at Colonies S and J from two groups of individuals, vacci-

TABLE 3.—COMPLEMENT-FIXATION TEST ON CONTROL GROUP.
(Age, over 21 years.)

Name.	Blood samples collected.		
	1-11-38	2-21-38	4-20-38
I. W.	1 : 4	1 : 4	No sample
D. S.	1 : 8	1 : 8	1 : 4
E. N.	1 : 4	1 : 4	1 : 4
P. S.	1 : 4	1 : 4	1 : 2
E. K.	0	0	0
J. M.	1 : 2	0	0
J. A.	1 : 2	0	1 : 2
A. W.	1 : 4	1 : 2	No sample
M. R.	1 : 4	1 : 2	No sample
M. M.	0	0	0
L. G.	1 : 4	1 : 2	1 : 2
A. M.	No sample	0	0

TABLE 4.—NEW LISBON COLONY—VACCINATED GROUP.

Complement-fixation test on blood samples collected.						
Name.	10-29-36	12-22-36	Sickness.	10-4-37	2-14-38	Sickness.
<i>Complete Fixation in Serum Dilutions.</i>						
K. G.	0	1 : 4	U. R. I.	1 : 8	1 : 8	Cold
S. K.	1 : 4	1 : 4	U. R. I.			
J. C.	1 : 32	1 : 64	U. R. I.	1 : 8	1 : 32	Colds
G. R.	1 : 32	1 : 64	Colds			
G. D.	1 : 32	1 : 32	Colds	1 : 16	1 : 32	No U. R. I.
E. B.	1 : 8	1 : 32	U. R. I.			
J. S.	1 : 4	1 : 4	No U. R. I.	1 : 8	1 : 4	Cold
L. S.	1 : 4	1 : 4	U. R. I.	1 : 2	0	No U. R. I.
G. H.	1 : 32	1 : 32	Cold	1 : 8	1 : 4	No U. R. I.
C. B.	1 : 64	1 : 32	Colds			
E. P.	1 : 8	1 : 32	Colds	1 : 8	1 : 8	Colds
G. C.	1 : 4	1 : 8	No U. R. I.	1 : 8	1 : 16	No U. R. I.
F. C.	0	1 : 2	Colds	1 : 16	1 : 16	Colds
S. C.	0	0	Colds	1 : 2	1 : 2	Colds
W. P.	1 : 4	1 : 8	Colds	1 : 8	1 : 8	Colds
W. T.	1 : 4	1 : 8	No U. R. I.	1 : 4	1 : 4	No U. R. I.
C. M.				1 : 4	1 : 4	No U. R. I.
E. S.				1 : 16	1 : 32	Colds
W. C.				1 : 16	1 : 32	Colds
W. K.				0	0	No U. R. I.
C. B.				1 : 32	1 : 16	No U. R. I.
P. M.				1 : 4	1 : 4	Cold
W. M.				1 : 8	1 : 32	Cold
G. W.				1 : 2	1 : 2	No U. R. I.
B. B.				1 : 8	1 : 8	No U. R. I.

TABLE 5.—NEW LISBON COLONY—NON-VACCINATED GROUP.

Complement-fixation test on blood samples collected.						
Name.	10-29-36	12-22-36	Sickness.	10-4-37	2-14-38	Sickness.
<i>Complete Fixation in Serum Dilutions.</i>						
N. S.	1 : 32	1 : 64	Cold	1 : 64	1 : 64	No U. R. I.
F. G.	0	0	Cold	1 : 4	1 : 4	No U. R. I.
T. S.	1 : 4	1 : 4	U. R. I.	1 : 8	1 : 16	No U. R. I.
E. H.	0	0	No U. R. I.	0	0	No U. R. I.
E. P.	0	1 : 8	No U. R. I.	1 : 16	1 : 16	No U. R. I.
C. M.	1 : 8	1 : 8	Cold	1 : 4	1 : 4	No U. R. I.
G. W.	0	1 : 4	No U. R. I.	1 : 2	1 : 4	No U. R. I.
C. W.	0	1 : 8	Cold			
D. W.	0	0	No U. R. I.			
J. S.	1 : 16	1 : 8	No U. R. I.			
P. M.	1 : 8	1 : 16	No U. R. I.			
J. N.	0	1 : 16	No U. R. I.			
G. R.	1 : 4	1 : 4	U. R. I.			
P. A.	0	1 : 16	U. R. I.			
H. R.	0	1 : 8	Cold			
M. S.				0	0	Cold
T. J.				1 : 8	1 : 8	U. R. I.
P. P.				0	0	No U. R. I.
C. C.				1 : 8	0	No U. R. I.
H. W.				0	0	No U. R. I.
D. W.				1 : 8	1 : 8	No U. R. I.
R. J.				1 : 16	1 : 16	No U. R. I.

TABLE 6.—SKILLMAN COLONY—VACCINATED GROUP.

Complement-fixation test on blood samples collected.				
Name.	9-23-37	2-15-38	Clinical history.	
	Complete fixation in serum dilutions.			
A. B.	1 : 32	1 : 64	No illness	
B. H.	1 : 8	1 : 8	No illness	
B. C.	1 : 16	1 : 16	No illness	
M. B.	1 : 32	1 : 32	No illness	
S. C.	1 : 8	1 : 8	No illness	
M. F.	1 : 16	1 : 16	No illness	
J. A.	1 : 8	1 : 8	No illness	
O. F.	1 : 8	1 : 8	No illness	
W. B.	1 : 8	1 : 8	No illness	
A. B.	1 : 8	1 : 16	No illness	
E. C.	1 : 16	1 : 16	No illness	
I. B.	1 : 8	1 : 8	No illness	
S. B.	1 : 8	1 : 16	No illness	
J. W.	1 : 8	1 : 8	No illness	
H. C.	1 : 8	1 : 2	No illness	
M. D.	0	0	No illness	
A. H.	1 : 16	1 : 4	No illness	
E. A.	1 : 8	1 : 8	No illness	
B. D.	1 : 8	1 : 8	No illness	
S. G.	1 : 8	1 : 8	No illness	
E. H.	1 : 8	1 : 16	No illness	
E. G.	1 : 4	1 : 8	No illness	
S. M.	1 : 8	1 : 16	No illness	
	10-5-37	2-17-38		
M. C.	1 : 4	1 : 8	No illness	10-5-37 through 5-15-38
R. R.	0	0	No illness	10-5-37 through 5-15-38
P. D.	1 : 16	0	No illness	10-5-37 through 5-15-38
L. W.	1 : 4	1 : 2	No illness	10-5-37 through 5-15-38
J. B.	0	0	No illness	10-5-37 through 5-15-38
J. V.	1 : 2	1 : 8	No illness	10-5-37 through 5-15-38
M. C.	1 : 2	1 : 2	No illness	10-5-37 through 5-15-38
J. B.	0	1 : 4	No illness	10-5-37 through 5-15-38
C. C.	1 : 4	1 : 8	No illness	10-5-37 through 5-15-38
E. K.	1 : 4	1 : 8	No illness	10-5-37 through 5-15-38
G. B.	1 : 4	1 : 8	1- 3-38	common cold
G. B.	1 : 8	1 : 8	1-11-38	U. R. I. 99°
M. G.	1 : 2	1 : 4	2- 7-38	common cold
D. C.	1 : 4	1 : 4	3-10-38	common cold
H. C.	1 : 8	1 : 8	2-11-38	otitis media 102.4°
L. M.	1 : 2	1 : 8	3-14-38	U. R. I. 103.4°
V. D.	0	0	2-23-38	common cold
H. V.	1 : 4	1 : 8	12- 7-38	U. R. I. 102°
E. P.	1 : 4	1 : 8	1-17-38	common cold

TABLE 7.—SKILLMAN COLONY—NON-VACCINATED GROUP.

TABLE 7.—BRILLMAN COLONY			
Complement-fixation test on blood samples collected.			
Name.	9-23-37	2-15-38	Clinical history.
	Complete fixation in serum dilution.		
D. P.	1 : 16	1 : 16	No illness
M. D.	1 : 8	1 : 8	No illness
E. L.	1 : 32	1 : 32	No illness
R. S.	1 : 8	1 : 8	No illness
M. H.	1 : 8	1 : 4	No illness
A. S.	0	1 : 2	No illness
M. T.	0	0	No illness
F. S.	1 : 8	1 : 8	No illness
M. W.	1 : 8	1 : 8	No illness
M. M.	1 : 16	1 : 8	No illness
S. S.	1 : 16	1 : 16	No illness
G. S.	1 : 4	1 : 2	No illness
I. V.	1 : 16	1 : 16	No illness
I. M.	0	0	No illness
D. R.	0	1 : 2	No illness
B. M.	1 : 8	1 : 4	No illness
H. W.	0	0	Common cold
J. J.	1 : 2	0	Common cold
J. W.	0	0	Common cold
D. W.	1 : 16	1 : 16	Common cold
A. W.	1 : 4	1 : 8	1-15-38 bronchopneumonia
C. W.	1 : 4	1 : 4	Common cold
R. P.	1 : 4	1 : 4	No illness
E. H.	0	0	No illness
A. P.	1 : 2	1 : 4	No illness
D. S.	1 : 2	0	No illness

nated and non-vaccinated during the winter of 1937-38. In each group the sera were taken at the same time, and in all determinations there was little significant change in titer. This lack of change in titer is similar to that shown in Table 2 when the sera were obtained during and following a mild epidemic of respiratory infections, non-influenzal in nature.

Discussion. In these studies constantly low titers of complement-fixing antibodies were found in the same individual over a long period of time if no infection with influenza virus had occurred and even though they had suffered from other types of respiratory infection. Such low titers persisted among hospital personnel in a large urban center as well as in the more isolated State Colonies studied. The general constancy of the titer recorded even in the sera of these individuals studied for more than two years tended to confirm the value of the method.

Repeated vaccination with chick embryo tissue culture vaccine as prepared in large batches for injection⁵ did not affect the complement-fixing antibodies, probably for the reason mentioned by Fairbrother.^{3b} If the complement-fixing antigen is a soluble substance liberated during multiplication of the virus in the tissues it is also possible that the use of infected mouse lung rather than chick embryo tissue culture vaccine might result in an increase in the complement-fixing antibodies. The effect of such vaccine has not been studied since mouse lung vaccine produces antibodies to the lung protein. However, vaccine derived from chick embryo tissue cultures following parenteral injection produced characteristic increases in the neutralizing properties of sera.* By the same route it also produced in mice immunity to the virus injected, as well as cross-immunity to other strains of human influenza virus.

In a few instances marked elevation in titer of complement-fixing antibodies studied in the sera of individuals following hospitalization established the cause of their respiratory infections as epidemic influenza. Such increases were absent following other types of respiratory infection. By such studies future epidemics of respiratory disease may be more satisfactorily classified as to etiology.

Summary. 1. A study over a 2-year period of complement-fixing antibodies in the sera of individuals vaccinated with chick embryo tissue cultures of active human influenza virus and in the sera of a similar group of non-vaccinated individuals is recorded.

2. In discussion of the complement-fixation test, the titration of the antigen against a known positive serum and the employment of a constant number of antigenic units is suggested.

* Further comparisons are now being made of the complement-fixing antibody titers and the neutralizing antibody titers on the same sera, both before and after vaccination of human beings with chick embryo tissue culture vaccine.

3. The value of repeated complement-fixation tests during and following acute respiratory infections for the diagnosis of epidemic influenza is again emphasized.

We are indebted to the Department of Institutions and Agencies of the State of New Jersey for their interest and coöperation in these studies.

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BOOK REVIEWS AND NOTICES.

ENDOCRINE THERAPY IN GENERAL PRACTICE. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin, etc. Pp. 192; 39 illustrations. Chicago: The Year Book Publishers, Inc., 1938. Price, \$2.75.

THE author has attempted a concise abbreviation of the current knowledge of endocrinology. It is not surprising, then, to find statements which might be questioned. What is surprising is the author's success in presenting the most sound and clear rationale of endocrine therapy which the Reviewer has seen. The recommendation of diets relatively low in carbohydrate and high in fat for diabetics is not the common practice today. (The author may suffer from them more than the patients.) For the practitioner seeking light in the fog of modern endocrinology this book is strongly recommended.

• F. L.

A SYMPOSIUM ON CANCER. Addresses by LEIV KREYBERG, CLARENCE C. LITTLE, MADGE T. MACKLIN, EDGAR ALLEN, HOWARD B. ANDERVONT, JAMES EWING, GIOACCHINO FAILLA, HENRI COUTARD, WARREN H. LEWIS, STANLEY P. REIMANN, JAMES B. MURPHY, and EMIL NOVAK. Given at an Institute on Cancer Conducted by the Medical School of the University of Wisconsin. Pp. 202; illustrated. Madison: The University of Wisconsin Press, 1938. Price, \$3.00.

THESE 17 papers by 12 well known authors on various aspects of the cancer problem cover a wide range: from genetic and external factors of causation, through various methods of study of the cancer cell—both in the exploration of its nature and in the diagnosis of individual cases—to clinical diagnosis and treatment (one paper each) and the relation of cancer to public health. The contributors, all of whom have done notable work in the laboratories or clinics of this country and Europe, have wisely chosen to expose phases of the problem in which they are especially interested and experienced, rather than to attempt a survey of the whole cancer problem. Details of the individual communications can hardly be considered here; but we can state without reserve that, impossible though it may be to cover the entire subject in such a symposium, yet these papers constitute the best collective statement of very recent progress in cancer research that we have been privileged to read.

E. K.

THE ETIOLOGY OF TRACHOMA. By LOUIS A. JULIANELLE, Chairman of the Trachoma Commission, Washington University, St. Louis. Pp. 248; 10 plates (3 in color). New York: The Commonwealth Fund, 1938. Price, \$3.25.

THE voluminous literature on the etiology of trachoma makes this book a very welcome edition to everyone interested in the subject. It is not a textbook on trachoma, and does not give any consideration to the treatment of this disease. It is a thorough compilation of all of the experimental work done on the cause of trachoma, including the author's own brilliant researches, and contains a complete bibliography.

F. A.

FRACTURES OF THE JAWS. By ROBERT H. IVY, M.D., D.D.S., F.A.C. Professor of Maxillo-Facial Surgery, School of Medicine and Graduate School of Medicine, and of Clinical Maxillo-Facial Surgery, School of Dentistry, University of Pennsylvania, etc., and LAWRENCE CURT A.B., M.D., D.D.S., F.A.C.S., Assistant Professor of Maxillo-Facial Surgery, Graduate School of Medicine, and School of Dentistry, University of Pennsylvania, etc. Pp. 192; 199 illustrations. Second edition thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$4.

It gives me great pleasure to express commendation of this work. stated in the Preface, it represents the knowledge acquired from many years of experience by the co-authors in several large hospitals. Both authors are oral surgeons as well as graduates in dentistry—a happy combination for a patient with a broken jaw. Chapters on anatomy of the facial regions, the complications of fractures here, roentgenograph and the dietary management of such cases are valuable supplements. An especially good feature of the treatment of fractures of these bones is the simplicity of the armamentarium, as compared to the many complex and expensive splints now on the market. This compact, practical treatise is a real addition, valuable alike to student and teacher. E. E.

JACOB HENLE: ON MIASMATA AND CONTAGIA. Translated by GEORGE ROSEN, M.D. Pp. 77; 1 illustration. Baltimore: The Johns Hopkins Press, 1938. Price, \$1.00.

THIS translation, reprinted from the Bulletin of the Institute of the History of Medicine, is an extremely important paper, written by one of the most influential 19th century Germans in medicine. Today Henle is too much known through the loops in the kidney that bear his name and too little for the important service that he performed in establishing and applying to human anatomy the newly discovered cell doctrine and preparing the way for a correct knowledge of the nature of infection—the subject of this discourse. This short article is not only a valuable milestone in the history of the theory of infection but also affords an interesting study of logical reasoning that produced important results without presenting any new discovery. It is a welcome addition to a library of medical history. E. K.

EXPERIENCE IN THE MANAGEMENT OF FRACTURES AND DISLOCATION (Based on an Analysis of 4390 Cases). By the Staff of the Fracture Service, Massachusetts General Hospital, Boston. Under the General Editorship of PHILIP D. WILSON, M.D., Surgeon-in-Chief, Hospital for Ruptured and Crippled, New York; Clinical Professor of Orthopedic Surgery, College of Physicians and Surgeons, Columbia University, etc. Twenty-three Contributors. Pp. 1036; 1419 illustrations (of which 119 are line tracings of Roentgenograms in Case Reports). Philadelphia: J. B. Lippincott Company, 1938. Price, \$15.00.

THIS book is unique throughout. The authors have recognized that there are many excellent treatises on the principles and practice of the treatment of fractures and dislocations; but they have endeavored to go, and I think very satisfactorily have gone, one step further and have applied specific and individual types of treatment to every kind of fracture met by them in their hospital service. Their data are based on experience with 4390 fractures and dislocations, treated and followed throughout until discharged. The writers very properly regard this extensive contribution as a compilation and collection of material which can be used for further study in arriving at even further conclusions helpful for future patients.

Especially valuable are the excellent follow-up reports of the final results, emphasizing the facts concerned with the poor results, let the blame fall where it may. A numerical scale of rating helps a great deal in visualizing the patients' results.

As the Preface honestly states there are faults of space, allotments, disagreements of minor importance in statistics and other minor criticisms that are insurmountable where there are several authors. The illustrations are many, and in most cases well chosen and clearly descriptive. The serial tracings are especially helpful. It is difficult to limit a work of this sort to a simple report. The technique of open or operative treatment should, I think, be excluded entirely. The indications for and the results of the same are germane.

An honest and successful effort has been made to give readers interested in fractures a valuable and comprehensive reference book based upon careful, thorough and extensive study of a sufficiently large number of cases from which to draw useful conclusions.

E. E.

A DIABETIC PRIMER FOR CHILDREN. By ALFRED E. FISCHER, M.D., Adjunct Pediatrician and Chief of the Children's Diabetic Clinic, Mount Sinai Hospital, New York City, etc. Pp. 53 (multigraphed). Second edition. Privately published. Obtainable from Dr. Alfred E. Fischer, 73 East 90th Street, New York City. Price, 75 cents.

THIS booklet should prove useful in the care of children with diabetes. The material is based entirely on accepted theories and plans of treatment and can be placed in the hands of the patient without hesitation. The first part of the booklet is devoted to telling the child the nature of his defect and what it will lead to if he does not take care of himself. This is followed by information about diet, insulin and general care. In a few instances the wording seems as though it would be a little difficult for a child to understand, but on the whole the language is simple.

R. R.

OUTLINE OF ROENTGEN DIAGNOSIS. An Orientation in the Basic Principles of Diagnosis by the Roentgen Method. By LEO G. RIGLER, B.S., M.B., M.D., Professor of Radiology, University of Minnesota, Minneapolis. Atlas Edition. Pp. 212; 254 illustrations shown in 227 figures presented in drawings and reproductions of Roentgenograms (Figs. 6 to 51 and 55 to 72 are drawings in an original technic by JEAN E. HIRSCH). Also Exclusive Text Edition from which the Atlas of Roentgenology has been omitted but to which all figure references have been retained in the text. Philadelphia: J. B. Lippincott Company, 1938. Price, Atlas Edition, \$6.50; Student's Edition, \$3.00.

THIS text is a comprehensive outline of Roentgen diagnosis which is admirably suited for teaching. Based upon a series of lectures developed by the author for undergraduate teaching, it presents a very extensive subject in synopsis form.

The book is divided into 11 "sections," each devoted to one portion of the body; for example, thorax, digestive tract, skull, and so forth. The material is handled in outline form. The basic and essential diagnostic criteria are tabulated in numerical order, little attention being given the atypical roentgen manifestations of the more common diseases. Rare and unusual conditions have not been included.

By publishing this work in two forms the author and publishers have considered the question of expense. The student's edition contains no

illustrations; the atlas edition is better bound and includes 227 illustrations arranged in atlas form. The illustrations appear as positive reproductions of original roentgenograms. Their detail is excellent and their legends satisfactory.

Not intended for reference purposes, the books will find their greatest application in undergraduate and graduate teaching.

P. H.

THE HORSE AND BUGGY DOCTOR. By ARTHUR E. HERTZLER, M.D. Pp. 322; illustrated. New York: Harper & Brothers, 1938. Price, \$2.75.

THIS book has been one of the "best sellers" for months, and, from several points of view, deservedly so.

E. K.

HANDBOOK OF HISTOLOGICAL AND CYTOLOGICAL TECHNIQUE. By R. R. BENSLEY, and S. H. BENSLEY, Department of Anatomy, The University of Chicago. Pp. 165. Chicago: The University of Chicago Press, 1938. Price, \$2.00.

THIS book is a combination of routine cytological and histological methods for the beginner, and special methods. The latter appear to be a worthwhile collection; the former are not up to date in a number of cases and cannot be enthusiastically recommended for beginners. The dogmatic style in giving instructions seems excusable, in such a handbook. The book is loose-leaf, and perhaps it will be improved in the future by the issuance of revised leaves. If not, there seems to be no justification for this binding.

N. S.

ALICE IN VIRUSLAND. By PAUL F. CLARK, Professor of Bacteriology, University of Wisconsin Medical School. Pp. 23; 5 illustrations. Madison, Wis.: Society of American Bacteriologists, 1938. Price, \$1.00.

THIS latest parody in the regular Alice tradition is excellent fooling for the medico, which is more than can be said of most 20th century Alices. To be pitied, indeed, is the reader who is "not amused," and few are there who will not be exposed to considerable sound wisdom in the reading process.

E. K.

ZUM KREBSPROBLEM UND VERWANDTEN GEBIETEN. Infektion, Regeneration, Zellmutation, Befruchtung. By DR. FRITZ NIEDERMAYER, Chefarzt und Leiter der Chirurgischen Abteilung des Krankenhauses Passau. Pp. 166. Wien: Franz Deuticke, 1938. Price, Paper, M. 5.00; Bound, M. 7.00.

THE author of this booklet appears to be a busy surgeon who two years ago published a monograph on "The Cancer Problem. Thoughts of a Practitioner." In his present paper he defends his previous hypotheses against his numerous critics who are mentioned by name, restating and elaborating his views. Reducing his theory to essentials, he believes that the cancer cell is the result of copulation, or fusion, through previous phagocytosis, of two heterogeneous somatic cells, of which one is an epithelial or connective tissue cell, the other a cell of the reticulo-endothelial system! This is by no means the most fantastic speculation in this very very uncritical composition, which on almost every page discloses the author's lack of training in the fundamental sciences. The last chapter deals with the therapeutic management of cancer and is quite in keeping with the rest.

B. L.

X-RAYS AND RADIUM IN THE TREATMENT OF DISEASES OF THE SKIN. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University; Consulting Dermatologist, St. Luke's Hospital, etc. Pp. 830; 308 illustrations, 31 charts and 2 colored plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

THERE can be nothing but praise for the third edition of Dr. MacKee's book. Actually it is a new book which has been raised to almost encyclopedic proportions through the energy and ability of no less than 9 collaborators. Each is an expert in his line, whereby authoritative treatment has been secured for all phases of the treatment of dermatoses by Roentgen rays and radium as well as the principles underlying treatment. For example, the physics of Roentgen rays occupies no less than 15% of the entire book. Technique accounts for another 15%. To the biological effects of Roentgen and radium rays, 5% is devoted, and another 5% to histopathology. Altogether, about half of the book is thus devoted to the consideration of the basic science aspects of this specialty within a specialty; a phase that has been long awaiting systematic and authoritative treatment.

The remaining half of the book deals with the particularities in treatment of the various dermatological entities. The closing chapter, on the medicolegal aspects is contributed by a member of the bar and must be of inestimable value to any physician who uses Roentgen rays and radium. Each chapter is concluded by an extensive bibliography.

Photographs of cutaneous lesions are abundant and uniformly excellent, and are selected to the point. The same is true of the photomicrographs and colored plate in the section on histopathology. Graphs and diagrams have not been spared for clarifying the section on the physics of Roentgen rays and radium.

The book is clearly printed on enameled stock. Bold type headings of paragraphs lends to easy reference. In short, no pains have been spared by authors or publisher to make the book comprehensive, attractive, authoritative and sufficient. It is difficult to discover how it could be improved, the volume is in a class by itself in the very forefront of works of its sort.

F. W.

VITAMIN B₁ (THIAMIN) AND ITS USE IN MEDICINE. By ROBERT R. WILLIAMS, Sc.D., of the Bell Telephone Laboratories, New York City, and TOM D. SPIES, M.D., Associate Professor of Medicine, University of Cincinnati. Pp. 411. New York: The Macmillan Company, 1938. Price \$5.00.

THIS volume, essentially a review of the extensive literature dealing with the subject of vitamin B₁, is an attempt to bring some sort of order out of chaos. The question might be raised whether the time is yet ripe for such an attempt since the conditions of investigation in many aspects of this field are still so far from uniform as to make evaluation of much of the work almost impossible. For any review of the subject, therefore, to be helpful to the average reader, a very careful critical judgment must be applied to the selection and interpretation of the papers quoted. Such judgment has been exercised with greater success in the second half of this volume (which deals with the historical and experimental aspects of the subject) than is evident in the handling of the first section on vitamin B₁ in the practice of medicine. In this latter section there is also lack of emphasis in presentation of a tremendous amount of detail so that the reader will find it difficult to obtain any clear notion of what constitutes established fact concerning the clinical aspects of vitamin B₁ deficiency. The authors have, however, referred to a vast literature and for this reason the volume will prove a

valuable reference book to those familiar with the field. It will prove of considerably less value to the medical man in search of help in the application of available information to practical problems, and for whom, apparently, the book was in part designed.

K. E.

THE PRINCIPLES AND PRACTICE OF PERIMETRY. By LUTHER C. PETER, A.M., M.D., Sc.D., LL.D., F.A.C.S., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Graduate Hospital of the University of Pennsylvania, etc. Pp. 331; 222 illustrations and 5 colored plates. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$4.50.

THE fourth edition of this well-known text on perimetry is comparable to the earlier editions in scope and usefulness. As in these, some confusion may occur because of the author's preference for recording fields in the "anatomic fashion." The recent literature on the anatomy of the visual pathways has not been sufficiently covered and most of the literature cited dates prior to 1930.

F. A.

THE PHYSIOLOGY OF ANESTHESIA. By HENRY K. BEECHER, A.B., A.M., M.D., Instructor in Anesthesia, the Harvard Medical School; Anesthetist-in-Chief, the Massachusetts General Hospital. Pp. 388. New York: Oxford University Press, 1938. Price, \$3.75.

THIS very interesting monograph is based upon material presented in a course on the fundamentals of anesthesia at the Harvard Medical School. The author has succeeded well in describing "the response of the body to anesthetic agents and to anesthesia." Essentially this volume is a presentation of the physiology of anesthesia rather than a textbook of the practice of anesthesia. There are four main chapters, an excellent bibliography and a good working index. The theories of anesthesia are briefly discussed. Local and spinal anesthesia are reviewed from the standpoint of special effects. In the main the volume concerns itself with respiration and circulation during anesthesia, and with the organic effects of anesthetic agents. The Reviewer knows of no volume which covers quite the same ground as does this one or which does the job so well. It will immediately take its place among the valued monographs on anesthesia.

I. R.

WORKBOOK IN ELEMENTARY DIAGNOSIS. For Teaching Clinical History, History Recording and Physical Diagnosis. By LOGAN CLENDENING, Professor of Clinical Medicine, University of Kansas. Pp. 167; illustrated. St. Louis: The C. V. Mosby Company, 1938. Price, \$1.50.

THIS book is the attempt to carry over into clinical teaching the laboratory notebook method that has so well established its usefulness in the teaching of the fundamental sciences. There is given sufficient in the way of information and outline to serve as a guide for the fledgling clinician without, however, supplanting a more formal textbook. Yet brief though the presentation be, the author has nevertheless in most instances given the explanation of physical signs in the words originally used by those who first described them. Particularly to be commended is the well rounded covering of the subject, instead of the all too frequent overemphasis of examination of heart and lungs. Open to objection is the dismissal of auscultation of the abdomen with the single sentence: "Like children, the abdomen should be seen and not heard." What about fetal heart sounds? Perisplenic or

perihaptic frictions? Altered peristaltic sound? The book is warmly recommended to teachers of physical diagnosis (which the author aptly renames elementary diagnosis) for their consideration and use. R. K.

CANCER. With Special Reference to Cancer of the Breast. By R. J. BEHAN, M.D., DR. MED. (Berlin), F.A.C.S., Cofounder and Formerly Director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation, Pittsburgh, Pa. Pp. 844; 168 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, \$10.00.

THIS book was written for the clinician who wishes to enlarge his knowledge of the cancer problem. It is written for "the practitioner . . . whose practice is limited and whose collateral reading is not sufficiently extensive to familiarize him with the more important advances of cancer research and cancer treatment." Although originally begun as a treatise on "Cancer of the Breast" it has been enlarged so that in 29 chapters every phase of cancer has been reviewed. Much of the material reviewed in this volume is irrelevant and poorly chosen. As an example of this the author quotes Sugiura and Benedict as stating that organotherapy has no influence on the growth of cancer cells and one would suppose that he agreed with this statement. Nevertheless, he proceeds to discuss the effect of a wide variety of glandular extracts on cancer tissue.

The chapters on Cancer of the Breast are on the whole very well done and had the volume been limited to this subject it would have received only favorable comment from the Reviewer. As it is, it is a vade medium of cancer of the breast with additional chapters on biophysics and biochemistry, constitutional treatment and radiation. For those who wish a review which in large part is not critically done in the field of cancer research this volume will be useful. The contributions to this field are being made with such rapidity that one wonders whether a volume of this extent is worth while, for it is soon outdated. I. R.

NEW BOOKS.

Pediatric Symptomatology and Differential Diagnosis. By SANFORD BLUM, A. B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post-Graduate School. Pp. 500; 29 illustrations, including 1 colored plate. Philadelphia: F. A. Davis Company, 1938. Price, \$5.00.

Silicosis and Asbestosis. By Various Authors. Edited by A. J. LANZA, M.D., Assistant Medical Director, Metropolitan Life Insurance Company; Chairman, Industrial Hygiene Committee of the New York Tuberculosis and Health Association. Pp. 439; illustrated. New York: Oxford University Press, 1938. Price, \$4.25.

Diseases of the Ear, Nose and Throat. By FRANCIS L. LEDERER, B.Sc., M.D., F.A.C.S., Professor and Head of Department of Laryngology, Rhinology and Otology, University of Illinois College of Medicine, Chicago; Chief of the Otolaryngological Service, Research and Educational Hospital. Pp. 835; 457 illustrations and 16 colored plates. Philadelphia: F. A. Davis Company, 1938. Price, \$10.00.

The Functions of Human Voluntary Muscles. By NORMAN D. ROYLE, M.D., CH.M., F.R.A.C.S., Honorary Demonstrator of Anatomy, University of Sydney; Senior Orthopaedic Surgeon, Lewisham Hospital, Sydney, etc. Pp. 42; 11 illustrations. Sydney: Angus & Robertson, Ltd., 1938. Price, 3/6.

- Shock and Related Capillary Phenomena.* By VIRGIL H. MOON, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College; Director of Laboratories, Jefferson College Hospital, etc. Pp. 442; 30 illustrations and 5 charts. New York: Oxford University Press, 1938. Price, \$3.50.
- Die elektrischen Gruppen in Biologie und Medizin (with an English Summary).* By RUDOLF KELLER. Pp. 92; 9 illustrations. Zürich: Sperber-Verlag, n.d. (Price not given.)
- Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-penetrating Traumatic Injuries. A Clinical Study.* By ERIK WARBURG, M.D. With a short Biography of Oluff Borch (Olaus Borrichius) by TORBEN GEILL, M.D. Pp. 147; 18 illustrations. Copenhagen: Levin & Munksgaard, 1938. Price, Kr. 14.00. (London: Humphrey Milford; Oxford University Press. Price, 12s. 6d.)
- The March of Medicine.* Selected Addresses and Articles on Medical Topics, 1913-1937. By RAY LYMAN WILBUR, M.D., President of Stanford University. Pp. 280. Stanford University, Calif.: Stanford University Press, 1938. Price, \$2.75.
- The New International Clinics, Vol. IV, N.S. 1 (Old 48th), 1938.* Original Contributions: Clinics; and Evaluated Reviews of Current Advances in the Medical Arts. Edited by GEORGE MORRIS PIERSON, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 18 Collaborators. Pp. 349; many illustrations, 1 in color. Philadelphia: J. B. Lippincott Company, 1938.
- The Nervous System.* A Guide for Use With the Educational Sound Picture "The Nervous System." Prepared by JAMES A. BRILL, Director of Production, Erpi Classroom Films, Inc. In Collaboration with FREDERICK T. HOWARD, Advanced School of Education, Teachers' College, Columbia University, and RALPH W. GERARD, The University of Chicago. Pp. 30; 6 illustrations. Chicago: The University of Chicago Press, 1938. Price, 15c.
- Drug Addicts are Human Beings.* The Story of our Billion-Dollar Drug Racket. How we Created it and How we can Wipe it Out. By HENRY SMITH WILLIAMS, M.D., B.Sc., LL.D. With a Statement of the Narcotics Problems. By HON. JOHN M. COFFEE, of Washington (Reprinted from the *Congressional Record*). Pp. 273; illustrated. Washington, D. C.: Shaw Publishing Company, 1938. Price, \$2.50.
- Alice in Virusland.* By PAUL F. CLARK, Professor of Bacteriology, University of Wisconsin Medical School. Pp. 23; 5 illustrations. Madison, Wis.: Society of American Bacteriologists, 1938. Price, \$1.00. (Review, p. 264.)
- Modern Surgical Technic.* In 3 Volumes. By MAX THOREK, M.D., K.L.H. (FRANCE), K.C. (ITALY), Professor of Clinical Surgery, Cook County Graduate School of Medicine; Attending Surgeon, Cook County Hospital; Surgeon-in-Chief, The American Hospital, etc. With a Foreword by DONALD C. BALFOUR, M.B., M.D. (TOR.), LL.D., F.A.C.S., F.R.A.C.S., Head of Section in Division of Surgery, The Mayo Clinic; Director and Professor of Surgery, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, etc. Vol. 1, General Operative Considerations, Surgery of the Head and Neck, and Plastic Surgery; Vol. 2, Surgery of the Nerves, Vessels, Bone, Breast and Chest; Vol. 3, Abdominal Surgery, Hernia, Genito-urinary and Gynecologic Surgery. Pp. 2045; 2174 illustrations, originals principally by W. C. Shepard. Philadelphia: J. B. Lippincott Company, 1938. Price, \$33.00 per set.

Avian Tuberculosis Infections. By WILLIAM H. FELDMAN, D.V.M., M.S., Associate in Division of Experimental Medicine, Institute of Experimental Medicine; Associate Professor of Comparative Pathology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 483; 109 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, \$7.00.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynecology, and Other Special Subjects. Vol. IX. Mumps to Pneumothorax, Spontaneous. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C., S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., F. M. R. WALSH, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 805; 117 illustrations and 10 plates (1 in color). London: Butterworth & Co. (Publishers), Ltd., 1938. Price, \$12.00.

Mental Disorders in Urban Areas. An Ecological Study of Schizophrenia and Other Psychoses. By ROBERT E. L. FARIS, and H. WARREN DUNHAM. Pp. 270; 37 maps, 96 tables and 2 charts. Chicago: The University of Chicago Press, 1939. Price, \$2.50.

Scarlet Fever. By GEORGE F. DICK, M.D., D.Sc., Professor of Medicine, University of Chicago; Attending Physician, Billings Memorial Hospital, etc., and GLADYS HENRY DICK, M.D., D.Sc. Pp. 149; 8 colored plates and 4 charts. Chicago: The Year Book Publishers, Inc., 1938. Price, \$2.00.

The Wheel of Health. A Study of a Very Healthy People. By G. T. WRENCH, M.D. (LOND.). Pp. 146; 1 illustration. London: The C. W. Daniel Company, Ltd., n.d. Price, 6/-.

NEW EDITIONS.

Allergic Diseases. Their Diagnosis and Treatment. By RAY M. BALLYEAT, M.A., M.D., F.A.C.P., Associate Professor of Medicine and Lecturer on Diseases Due to Allergy, University of Oklahoma Medical School; Chief of the Allergy Clinic, University Hospital, etc. Assisted by RALPH BOWEN, B.A., M.D., F.A.A.P., Chief of Pediatric Section, Balyeat Hay Fever and Asthma Clinic, Oklahoma City, Okla. Pp. 547; 145 illustrations, including 8 in colors. Fifth edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1938. Price, \$6.00.

Urology. By DANIEL N. EISENDRATH, M.D., Consulting Urologist to the American Hospital, Paris, France; formerly Attending Urologist, Michael Reese and Cook County Hospitals, etc.; and HARRY C. ROLNICK, M.D., Attending Urologist, Michael Reese, Mt. Sinai, and Cook County Hospitals, Chicago, etc. Pp. 1061; 750 black and white illustrations and 12 in color. Fourth edition, entirely revised and reset. Philadelphia: J. B. Lippincott Company, 1938. Price, \$10.00.

Classic Descriptions of Disease. With Biographical Sketches of the Authors. By RALPH H. MAJOR, M.D., Professor of Medicine, University of Kansas School of Medicine. Pp. 727; illustrated. Second Edition. Springfield, Ill.: Charles C Thomas, 1930. Price, \$5.50.

PROGRESS OF MEDICAL SCIENCE

OPHTHALMOLOGY.

UNDER THE CHARGE OF
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OPTOCHIASMATIC ARACHNOIDITIS.

IN the last 10 years, increasing attention has been paid to the ocular syndromes caused by local arachnoiditis in the region of the chiasm and intracranial portion of the optic nerves, and especially to their diagnosis and surgical treatment. No single type or mode of loss of vision has been found to be pathognomonic of this lesion. Published case reports include practically every possible form of acute and chronic involvement of the chiasm or of the optic nerves anterior to the chiasm. No definite etiology has been assigned to the condition. It seems quite possible that some cases of acute retrobulbar neuritis have been subjected to intracranial surgery under the probably mistaken diagnosis of chiasmal or prechiasmal arachnoiditis. Some neurosurgeons are inclined to doubt either the existence of this lesion as a primary clinical entity or the efficacy of surgical intervention. Yet there seems to be rather conclusive evidence that certain hitherto hopeless cases of progressive optic atrophy can be benefited by the removal of obvious constricting fibrous bands around the nerves, even though the exact underlying etiology and pathology of these bands is not known. And it seems possible that ultimately a clear-cut syndrome may evolve which will enable the ophthalmologist to further reduce the number of optic atrophies which he must classify at present as of unknown etiology and not amenable to treatment. It would seem that sufficient data has been accumulated now in widely separated centers to warrant a review of our present knowledge of the subject.

According to Vail,¹³ the entity of chronic arachnoiditis was established in its generalized form by Quincke in 1893 and in its localized form by Schlesinger in 1898. In February, 1929, Cushing and Eisenhardt⁵ stated that, in a few cases explored because of a suspected suprasellar neoplasm, nothing was found but a local collection of slightly xanthochromic fluid, the evacuation of which led to a subsidence of symptoms. In such cases the presumptive diagnosis of chronic cisternal arachnoiditis was made, though Cushing seemed unwilling to regard such a diagnosis as proved in the absence of necropsy.

Apparently the first report confined to optochiasmatic arachnoiditis as a clinical surgical entity was that published by Balado¹ in 1929. In his case, progressive loss of vision for 6 months, pallor of disks with slight loss of substance, and a bitemporal type of defect in the fields of

vision led to an exploration of the chiasmal region. Localized arachnoiditis was the only lesion found. Histologic examination of a biopsy specimen of the arachnoid revealed a proliferation of the endothelial cells and some small calcareous nodules. The vision improved somewhat after the operation.

In 1930, Deery⁷ published the findings in 170 cases operated on in Cushing's Clinic during a 10-year period because of the presence of a chiasmal syndrome. He stated that in 13 cases (7.5%) the only positive finding was a definite thickening of the arachnoid with an abnormally large collection of fluid about the chiasm and optic nerves. Optic atrophy was present in 11 of these cases and choked disks in 2. Bitemporal hemianopsia was noted in 7 cases, homonymous hemianopsia in 2, and scotomas (probably central) in 4. Again there was hesitancy in accepting this lesion as a definite clinical entity. Deery noted that 2 similar patients with thickened arachnoid had proved to have syphilis. Later in the same year, Cushing⁴ reported a case with cecentral scotomas and irregular bitemporal contraction in which exploration revealed demonstrable thickening of the arachnoid constituting the cisterna chiasmaticus with a large accumulation of fluid. The vision failed to improve following evacuation of the fluid. Cushing stated: "The diagnosis of cisternal arachnoiditis, however, is one that I am exceedingly loath to make in the absence of postmortem examination, for one may be easily deluded, and not a few patients with symptoms ascribed to such a process have subsequently proved to have tumor." Also, Cushing was not willing to accept the etiologic relationship of nasal accessory sinus disease to this form of arachnoiditis. In the same year, in discussing the subject of cerebral pseudotumors, Frazier⁸ mentioned 5 cases with signs suggesting pituitary lesions and stated that they were improved after operation.

In 1931, Davis and Haven⁶ described three types of lesions in the intracranial arachnoid membrane, inflammatory, fibrous and hyperplastic. Included in their series were 2 cases with involvement of the prechiasmal portion of the optic nerves. In both of these cases, the lesion was of the fibrous type. One case, in which the possibility of Leber's hereditary optic atrophy was considered, showed only adhesions around the optic nerves. In the other case, in which vision was reduced to light perception only, an enormously dilated cisterna chiasmaticus was found. In both cases, histologic examination revealed marked thickening of the reticular structure of the arachnoid due to an increase in the fibrous elements with a moderate amount of leukocytic infiltration. Vision improved in both cases after surgery.

It will be noted that some reports emphasize only the adhesions around the chiasm and optic nerves, while others stress the dilatation of and accumulation of fluid in the cisterna chiasmaticus. The difference in these two points of view or two types of lesion is clearly brought out in two reports published in 1931. Heuer and Vail¹⁰ reported 4 cases of "chronic cisternal arachnoiditis" in all of which the cisterna chiasmaticus was markedly distended with fluid. In 1 of the cases, central scotomas with temporal contraction of the peripheral fields were present, in 2 concentric contractions, and in 1 total blindness. At operation, the fluid in the cistern was evacuated, the wall of the cistern was excised, and the chiasm and optic nerves were freed from adhesions. Vision improved in all cases. Craig and Lillie³ reported 8 cases of

"chronic local arachnoiditis" in all of which the presence of arachnoiditis with adhesions around the chiasm and optic nerves was noted. Bitemporal hemianopsia was present in 4 cases, homonymous hemianopsia with central scotoma in 3, and unilateral nasal hemianopsia in 1. Vision improved after operation in only 2 cases. Three cases came to necropsy. In 1 of these, necropsy revealed chronic basilar arachnoiditis with chronic local arachnoiditis and marked adhesions around the chiasm. In the other 2 cases, necropsy revealed basal meningitis with encephalitis. In 1 case, there was additional gliosis of the aqueduct.

Also in 1931, Vincent, Puech and David¹⁴ reported 7 cases of optochiasmatic arachnoiditis in which adhesions around the nerves were the outstanding findings. Central scotomas were present in 4 cases, concentric contraction in 2, and temporal contraction in 1. In 3 cases the vision was considerably improved after operation; in 3 cases it remained stationary; in 1 the loss of vision progressed in spite of surgery. The authors felt that the characteristic features suggesting the diagnosis of chiasmal arachnoiditis were: 1. rapid loss of vision, at first with normal fundi and later with simple optic atrophy; 2, frequently central scotomas early, bitemporal hemianopsia rare or late; 3, mild evidences of infection and an episodal rather than a steadily progressive loss of vision; 4, normal sella; and, 5, absence of signs of pituitary insufficiency.

Since these early reports, a number of cases (approximately 130) have been cited in the literature. A few points of interest are worthy of especial note. In 1937, Rubino¹¹ reported 5 cases which he diagnosed as optochiasmatic arachnoiditis. He treated 3 of these medically, with improvement in 1 and no improvement in 2, and 2 surgically with improvement in both. He thought that better results were to be expected from surgery if hydrocephalus of the chiasmal cistern was found and not merely adhesions. In the medical treatment he employed fibrolysin and iodides. He felt that if progressive loss of vision continued under medical treatment, surgery should be instituted.

In 1937, Hausman⁹ suggested that syphilitic arachnoiditis in the neighborhood of the chiasm might be the cause of some of the cases of progressive atrophy in syphilitics in whom a definite diagnosis of tabes cannot be established. He reported 4 cases, in each of which there was a typical chiasmal syndrome with primary optic atrophy and heteronymous field defects. Three were treated medically and 1 surgically. In this 1 case adhesions were found around the chiasm and were separated. This was the only case that showed any improvement in vision and fields. He concluded, therefore, that surgical treatment was the method of choice in cases of this type, especially when blindness is imminent. A fifth case showed bilateral papilledema with concentric contraction of the fields without increased intracranial pressure or dilatation of the ventricles. Necropsy on this case revealed diffuse perichiasmal gummatous meningitis with definite syphilitic exudate into the chiasm. Other syphilitic lesions were present in the brain also.

In 1938, Vail reported 4 more cases of "optochiasmatic arachnoiditis." In 3, the diagnosis was confirmed at operation. The fourth case was treated with injections of typhoid vaccine intravenously, large doses of sodium salicylate, frequent spinal drainage, and sodium iodide intravenously. Recovery was satisfactory. One of the cases which showed at operation an accumulation of fluid in the chiasmal cistern later developed typical findings of multiple sclerosis. Vision improved only

slightly following surgical intervention. Vail suggested that the characteristic appearance of the optic disks in cases of chiasmal arachnoiditis is that of a mixed atrophy, an atrophy of simple type with narrowing of the retinal vessels or with mild blurring of the disk margins.

In a review of the subject of retrobulbar neuritis, Schieck¹² accepts the views of Burgeois, Puech and their coworkers on the etiology and pathogenesis of optochiasmatic arachnoiditis. They state that the cerebrospinal fluid is contained not in the subarachnoid space but between two layers of arachnoid, one adherent to the dura and the other adherent to the pia. This space between the two layers of the arachnoid widens in some places as in the chiasmal cistern. Adhesions between these two layers may follow even mild inflammations and can result in a ballooning out of the normally wider spaces sufficient to cause pressure on the chiasm and optic nerves. Optochiasmatic arachnoiditis, they state, may arise as a late sequence of trauma such as skull fracture, as a complication of nasal accessory sinus disease, mastoiditis or petrositis, or as a sequel of encephalitis either non-specific or due to lues, of multiple sclerosis or of tuberculosis.

In 1937, Bollack, David and Puech² published a very complete review of our knowledge to date on the subject of optochiasmatic arachnoiditis. On the basis of 129 cases, 63 collected from the literature and 66 of their own, these authors summarized the clinical symptoms of optochiasmatic arachnoiditis. The primary symptom is loss of vision, which may occur suddenly or gradually, usually the latter, and which is usually unilateral at first though both eyes may be involved immediately. Central vision may be good but usually is considerably reduced, and blindness may be complete in one or both eyes. Defects in the peripheral fields of vision are the most constant findings. The three most frequent types are: 1, temporal or bitemporal hemianopsia; 2, concentric contraction; 3, central scotomata; less frequent findings are: 4, nasal contraction; 5, homonymous hemianopsia; and, 6, altitudinal contraction.

Bitemporal hemianopsia occurs in only about 17% of the cases of chiasmal arachnoiditis and is usually later in development, more-irregular in outline, and more atypical in character than in tumors in the region of the chiasm. It may be accompanied by concentric contraction of the residual fields and by central scotomata. Bitemporal hemianopsia for colors is not an early sign of chiasmal arachnoiditis.

Concentric contraction of the fields of vision occurs in about 23% of the cases. It may be slight or extreme in degree. It is usually irregular in type and may be accompanied by temporal contraction, central scotomata, or homonymous hemianopsia.

Central scotomata are found in about 31% of the cases and are therefore the most frequent finding. They occur usually early in the course of the disease. They are usually bilateral and absolute and usually large. They may be of cecocentral type, directly central, or paracentral. They are associated often with temporal hemianopsia, homonymous hemianopsia, nasal hemianopsia, or concentric contraction.

Nasal contraction is usually an early phase of concentric contraction but it may be more definitely a nasal or binasal hemianopsia. It occurs in about 7% of the cases. It indicates involvement of the prechiasmal portion of the optic nerves rather than of the chiasm. It is often accompanied by central scotomata.

Homonymous hemianopsia occurs in about 5% of the cases and is associated usually with central scotomata or with considerable reduction of central vision. It indicates a rather diffuse lesion with involvement of the optic tracts as well as of the optic nerves.

Altitudinal contraction occurs in about 5% of the cases. It is usually of inferior type but occasionally involves the upper fields. It may be associated with central scotomata.

In 12% of the cases, the fields of vision were either normal, not reported, or could not be obtained because of poor vision.

Ophthalmoscopically, the optic disks are found to be normal in 10% of the cases, show primary optic atrophy involving the whole disk in 38%, temporal segmental pallor in 7%, partial horizontal atrophy in 4%, post-inflammatory optic atrophy in 10%, post-edematous optic atrophy in 6%, simple hyperemia in 7%, choked disks in 10%. In 8% the appearance of the disks is difficult to classify. It must be remembered that the aspect of the disks may be different in the same case at different stages of the disease. The presence of choked disks probably indicates that the arachnoiditis has extended toward the posterior part of the base and has invaded the cisterna magna or else that there is an added ventricular hydrocephalus.

Rather rarely, involvement of the third, fifth or sixth nerves, or nystagmus, occurs in association with the optic nerve lesions of chiasmal arachnoiditis. Headache, usually bifrontal or fronto-temporal, may be an early symptom and may precede the loss of vision. It may be accompanied by somnolence and occasionally by vomiting and vertiginous attacks. Rarely, polydipsia, polyuria and obesity occur, or an atypical adiposo-genital syndrome. Convulsions or mental changes may occur in rare cases. In most instances, however, the symptoms and findings are confined to the eyes and examination of the rest of the nervous system yields negative results. Anosmia, facial paralysis, or affections of the eighth nerve are found occasionally. The spinal fluid is usually normal. At times, a mild increase of cells and protein is found.

Roentgenograms of the sella turcica should be normal in cases of chiasmal arachnoiditis. Exceptionally, enlargement of the tuberculum sellæ, enlargement of the sella with thinning of the posterior clinoids, atrophy of the anterior clinoids and of the small wing of the sphenoid have been reported. But, in the main, the diagnosis has not been verified in these cases. Essentially, the optic foramina are always normal. However, 1 case of proven cystic serous meningitis showed enlargement of both optic foramina and a deformity of the sella characteristic of glioma of the chiasm. Exceptionally, the roentgenograms reveal some spots of calcification. Roentgenograms of the skull may reveal increased vascularity or spreading of the sutures. Roentgenograms of the sinuses may reveal cloudiness of one or more of the sinuses or perisinusitis. Ventriculograms are normal usually. Occasionally, they show mild internal hydrocephalus. In a few instances the ventricles are seen to be small and most of the air is in the subarachnoid spaces. Exceptionally, air will be seen to have entered a subarachnoid cyst.

In general, the purely ocular symptomatic forms of chiasmal arachnoiditis may be classified into three groups: 1, the syndrome of axial neuritis, acute or chronic (25% of the cases); 2, the syndrome of simple atrophy (13% of the cases); and 3, the chiasmal syndrome (15% of

the cases). In the remaining 47% of the cases, the ocular lesions are more atypical or are associated with signs of involvement of other parts of the brain.

The differential diagnosis of chiasmal arachnoiditis from other lesions affecting the prechiasmal and chiasmal portions of the optic nerves is very difficult to establish positively before operation. The diagnosis may be suggested by the rather atypical course of the disease and its tendency to advance in successive episodes, by the association of evidences of inflammation of neighboring structures, by the etiologic factors of trauma, sinusitis or encephalitis, and by the fact that roentgenograms of the head, ventriculograms and spinal fluid are normal. Cases that develop in the form of acute axial neuritis must be differentiated from multiple sclerosis, in which the lesion is more often unilateral and has a tendency to rapid spontaneous improvement; from neuromyelitis optica, in which characteristically there is rapid development of the signs of a progressive myelitis; from encephalitis, especially if this is atypical in its course or if it is complicated by arachnoiditis, and from the retrobulbar neuritis due to sinusitis, which is especially difficult since sinusitis may be the cause of the arachnoiditis.

Cases that develop in the form of chronic retrobulbar neuritis must be differentiated from toxic amblyopia, in which the course is normally more gradual and uniformly progressive and in which the toxic substance is usually known; from Leber's disease, in which the family history is of the greatest importance, and from tumors in the basofrontal and prechiasmal regions, in which the roentgenographic findings and ventriculogram aid in the diagnosis.

Cases that develop in the form of simple optic atrophy with concentric contraction of the peripheral fields are to be differentiated particularly from atrophies due to syphilis.

Cases that present the typical chiasmal syndrome must be differentiated from the various types of tumors occurring in this region.

Medical treatment may be tried in the early stages of the disease. The remedies suggested are cyanide of mercury, iodides, sodium salicylate, urotropin, neurotropic vaccines, vitamin B₁, and Roentgen ray. If these measures fail to control the progress of the disease, surgical intervention is justified.

On exploration, lesions of three types may be encountered: 1, arachnoiditis; 2, serous meningitis; and, 3, optic atrophy. The term arachnoiditis is applied to the interlacing of arachnoidal fibers which ensheathes the optic nerves and the chiasm and fixes them to the neighboring structures, especially to the large vessels. This is associated often with engorgement of the adjacent veins. The arachnoidal network may be composed of: 1, very fine filaments; 2, solid, well-limited bands which compress the nerves; 3, a sheet of arachnoiditis masking the entire region; 4, calcareous plaques may be added to the plastic formations; 5, arachnoidal adhesive bands with associated vascular bands. Serous meningitis of the chiasmal cistern with arachnoidal cysts also may appear under several forms: 1, a suprachiasmal arachnoid cyst which may simulate a tumor; 2, an intrasellar arachnoid cyst which may give rise to a forward bowing of the sella similar to that seen in glioma of the chiasm; 3, multiple cysts; and, 4, gelatinous tissue. In the cases which are designated as optic atrophies, the nerves are atrophic but no definite arachnoidal adhesions are found. Histologic

examination of the optic nerves in any of these types of arachnoiditis reveals peripheral neuritis with demyelination and atrophy of a certain number of nerve fibers.

In a series of 254 explorations of the chiasmal region which were analyzed by Bollack, David and Puech, 71 (27%) proved to be chiasmal arachnoiditis. In a series of 95 cases of chiasmal arachnoiditis, the immediate mortality was about 7.5%. Recurrence of the condition occurred in two forms, an immediate, which started within 12 to 15 days following surgery, and a late, which started several months after surgery. Recurrences of each of these types were noted in 3 cases, a total of 6%. Of the cases collected from the literature, 46% showed improvement after operation, and in 20% the operation was a complete failure. Definite improvement was noted in 28% of their own cases. The results were found to be poor usually in cases in which the symptoms were of several years' duration, although improvement was noted even in a few of these. The best results were noted in cases of less than a year's duration. Cases operated on within a few weeks of the onset of loss of vision have good results usually, but in such cases it is not at all certain that improvement in vision would not have occurred under medical treatment. Of the 19 good results obtained by Bollack and his associates, 11 were in cases of less than a year's duration. However, not all cases of less than a year's duration improve. Cases with very poor vision or even complete blindness may improve if the blindness is not of too long standing. Ophthalmoscopically visible atrophy of the optic nerves is not a contraindication to surgery, since some cases improve in the presence of apparently complete atrophy. Edema of the disks or normal disks are usually good prognostic signs. Of the 19 good results noted by Bollack, 5 had normal optic disks. Of 29 improved cases collected from the literature, 9 had shown impairment of central vision without defects in the peripheral fields, 8 had shown defects in the peripheral fields without loss of central vision, and in 12 both central and peripheral vision had been involved. In Bollack's series of 19 improved cases, 10 had shown loss of central vision without peripheral field defects, 3 had shown peripheral field defects only, and in 6 both central and peripheral vision had been affected before operation. The associated symptoms such as headaches, somnolence, epileptiform attacks, mental disturbances, and diabetes insipidus, may improve after operation also.

It is of some interest to note the type of lesion found in the cases in which the results of operation were favorable. Of 25 improved cases collected from the literature in which the data were available, 12 showed arachnoidal adhesions only, 3 purely cystic lesions, and 13 a mixed type of lesion. Among 14 improved cases in the series of Bollack and his coworkers, arachnoidal adhesions only were found in 3, cysts alone in 3, and mixed lesions in 9. It is impossible to tell from the gross appearance of the optic nerves at operation whether improvement in vision will be obtained.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 19, 1938

The Influence of the Erythrocytes Upon the Oxygenation of the Blood of Fish. E. C. BLACK, LAURENCE IRVING and R. W. ROOT (Martin Biological Laboratory, Swarthmore College, and College of the City of New York). The respiratory pigments of vertebrates and invertebrates are in general half saturated with oxygen at pressures lower than 10 mm. Such ease of saturation favors oxygenation, but it means that the unloading of oxygen into the tissues is not provided with a pressure adequate to secure diffusion into the tissues. The introduction of CO₂ into the blood of fishes, however, raises the pressure of oxygen at 50% saturation in proportions of from 1 to 6 mm. for each added millimeter of CO₂. The bloods of 3 fresh-water and 3 marine fishes have been examined. In 5 cases the effect of CO₂ in raising the pressure of oxygen necessary for half saturation is practically abolished by hemolysis; in 1 it is greatly diminished by hemolysis.

The effect of CO₂ has been attributed to its influence as an acid in diminishing the affinity of hemoglobin for oxygen. But inasmuch as CO₂ does not affect the hemoglobin in hemolyzed blood, it appears that it is only the hemoglobin in the corpuscle which is sensitive to the influence of CO₂. The sensitivity must be due primarily to the operation of CO₂ upon the intact corpuscle. While ultimately it is the affinity of hemoglobin for oxygen which makes possible the respiratory transport of oxygen, these specific properties of the blood of fishes are in the first analysis attributable to the behavior of the erythrocytes.

The Carbohydrate of the Gonadotropic Hormone of Pregnancy Urine. S. GURN, C. BACHMAN and D. W. WILSON (Laboratories of Physiological Chemistry, and Obstetrics and Gynecology, University of Pennsylvania). A modified process has been developed by which highly active gonadotropic hormone preparations can be obtained from early pregnancy urine. After preliminary adsorption upon benzoic acid by the Katzman-Doisy technique, the crude hormone so obtained is further purified by extraction with 50% alcohol at pH 6, followed by addition of 2 volumes of alcohol to the alcoholic extract. The resulting precipitate is then extracted with 50% alcohol at pH 4.8 and the hormone thrown out of solution by the addition of an equal volume of absolute alcohol. The resulting product has been found active in 0.35-1.0 γ , thus containing 1000-3000 minimal ovulating doses per mg. when assayed by the Friedman technique.

These preparations contain carbohydrate, hexosamine, acetyl and polypeptide groups while pentose, uronic acid and keto-hexose appear to be absent. As has been previously observed by Meyer, the hormone appears to have the chemical and physical properties of a mucoid.

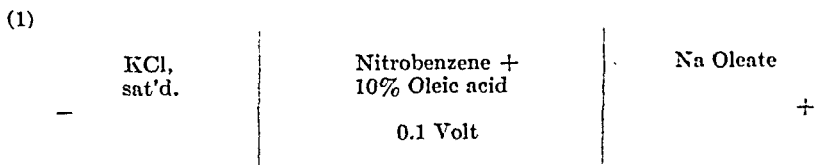
The molecular ratios of reducing sugar to hexosamine suggest the presence of carbohydrate units consisting of 1 hexosamine and 2 hexose groups. By means of the carbazole and orcin reactions it has been established that the non-hexosamine carbohydrate of several of our best preparations is entirely galactose. The ratio of galactose (determined by the carbazole method) to hexosamine is 2 to 1.

The Electromotive Forces Produced by Alkaloids in Oil Batteries.
R. BEUTNER (Department of Pharmacology, Hahnemann Medical College). In several publications, some of which date back as much as 27 years, I have demonstrated the electrode-like properties of water-insoluble electrolytic conductors. An oil mixture containing, for example, cresol and an organic acid acts as an electrode which is reversible for various cations, while an oil such as toluidin is reversible for anions. An attempt is now being made to use such oil batteries for analytical purposes.

Just as a hydrogen electrode is used for measuring hydrogen ion concentrations, so also is it possible to measure the concentration of certain other ions in a solution by placing a suitable oil electrode in that solution, for example, alkaloidal concentrations in galenical preparations can thus be estimated.

The "oil" electrode which we used contained a mixture of nitrobenzene with 10% oleic acid; this mixture is filled into a cup which is attached to a calomel electrode. A cup-shaped electrode is immersed into a 0.1% solution of sodium oleate, or sodium benzoate. This solution is directly connected with another electrode and the E.M.F. is measured by means of an electrometer.

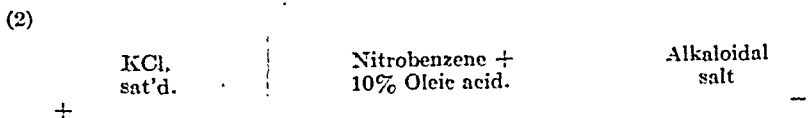
The measured system is therefore:



in which the positive pole is on the side of the sodium salt of the organic acid. To this organic salt solution we added varying small amounts of alkaloidal salts. This addition markedly decreases the E.M.F. of system (1), even in amounts as low as 1 to 1,000,000.

Such a drop in E.M.F. is specific for alkaloids and can be used for their determination.

The action of the alkaloidal salt is due to the fact that it produces the E.M.F. in the opposite direction. A system like:



has its E.M.F. in the opposite direction.

The E.M.F. of such systems as (1) and (2) is due to the potential differences located at the phase boundary of the nitrobenzene and the various watery solutions. The organic salt, sodium oleate, or an alkaloidal salt, penetrates more than an inorganic salt, but the sodium oleate carries positive sodium ions and the alkaloidal salt carries negative sulphate ions into the nitrobenzene. This explains their antagonistic action. The theory is explained in detail in the lecture and graphs are presented which show the observed relation between alkaloidal concentration and drop of the E.M.F. of system (1) after addition of alkaloids.

The powerful electrical action of alkaloids as observed in systems of this type suggests a possible explanation of their action.

We expect to study by a similar technique the concentration of alkaloidal hormones like epinephrine, histamine, acetyl-choline, and their presence in biological fluids.

The Long Persistence of Excitation at a Synapse. M. G. LARRABEE and D. W. BRONK (Johnson Research Foundation and The Institute of Neurology, University of Pennsylvania). The long persistence of an excitatory state in the central nervous system has usually been attributed to the continued arrival of impulses over delayed paths or long chains of neurons. It has been further assumed that each volley of impulses arriving at a cell in the central nervous system or in a sympathetic ganglion produces a discharge of but one impulse.

The present experiments show, however, that an excitatory state can persist for a long time in a synaptic region. The investigations have been made on the stellate ganglion of the cat—a structure in which there are no complex neuronal chains. We find that rapidly repeated preganglionic volleys produce a synaptic effect which lasts for many seconds or even minutes, as a result of which: 1, cells continue to discharge impulses for many seconds after the end of preganglionic stimulation; and, 2, more cells respond to a given preganglionic volley than before the conditioning stimulus. Because impulses entering the cell antidromically reduce rather than increase their responsiveness to preganglionic volleys and do not produce after-discharge, the long-lasting change in the properties of a ganglion is not attributable to previous activity of the ganglion cells themselves but rather to some alteration in the properties of the synaptic mechanism.

The long persistence of this change in properties of the synaptic region, which may be referred to as an excitatory state, requires some modification of the acetylcholine hypothesis for synaptic transmission. If excitation is due to liberation of acetylcholine from the terminations of the presynaptic fibers, it will be necessary to assume that it is not as rapidly destroyed as has been previously assumed. Or, on the other hand, it may be necessary to conclude that there are other accompaniments of presynaptic activity which leave long-lasting effects capable of producing excitation of the postsynaptic cells.

The Irritability Cycle of Nerve Cells for Excitation by Acetylcholine. D. W. BRONK and M. G. LARRABEE (Johnson Research Foundation and The Institute of Neurology, University of Pennsylvania). As a wave of propagated activity passes a given region of a nerve cell, that portion of the cell surface is electrically negative relative to an inactive region. Thereafter it becomes successively positive, negative, and again posi-

tive. Gasser and his associates have shown that the positive phase of these after-potentials is correlated with a state of the nerve in which it is less readily stimulated by an electric current; during the phase of the negative after-potential it is more irritable than before activity. These facts suggest that the after-potentials are useful indicators of the readiness with which nerve cells will respond to stimulation.

In the normal functioning of the central nervous system, however, excitation is generally accomplished by nerve impulses arriving at the synapses. Rosenbluth and Simeone (*Am. J. Physiol.*, 122, 688, 1938) maintain that this excitation is due to acetylcholine rather than to the action current of the presynaptic impulses and conclude that there is therefore no parallelism between after-potentials and synaptic excitation.

In order to settle this issue we have excited nerve cells in a sympathetic ganglion by continuous perfusion with appropriate concentrations of acetylcholine and have, at the same time, recorded the impulses they discharged into the postganglionic nerve. During such chemical excitation we have produced a further rapid excitation of the cells by repeated volleys of preganglionic and antidromic impulses. Following these periods of activity, we have observed the development of a large ganglionic positive after-potential. During the course of this after-potential, fewer cells were observed to respond. As the potentials decreased there was again a more active discharge of impulses, there being a close parallelism between the degree of inexcitability and the magnitude of the potential.

The positive after-potential is therefore a measure of the inexcitability of nerve cells for either electrical or chemical excitation and is, accordingly, a useful sign of the irritability of ganglia or groups of cells in the central nervous system.

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THE
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ORIGINAL ARTICLES.

THE HEALING OF CAVITIES.

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THE importance of cavitation of the lung in pulmonary tuberculosis has long been recognized, though more recently increased attention has been given to this subject, stimulated by the use of active methods of cavity closure. Physiologic and pathologic studies support the view that the same processes are at work in healing cavities whether methods involving active collapse are used or if spontaneous healing occurs. The latter possibility was first recognized by Laennec,⁴ whose knowledge was based on careful morbid anatomic studies. He thus describes the manner of cavity healing: "(a) Conversion of an ulcer into a fistula, lined, like all those which may exist without injuring the general health, by a membrane analogous to the tissues of the healthy body, or in another way (b) by means of a cicatrix more or less complete and consisting of cellular fibro-cartilaginous or semi-cartilaginous substance." Similar observations were made by Latham:⁵ "In examining by dissection . . . among many existing vomices we occasionally find the traces of a vomica healed. At the apex of the lung we find an indentation and descending from it for half an inch or an inch, a thick perpendicular line of tough ligamentous substance. Sometimes this substance, by being pulled asunder, is discovered to contain the remains of a cavity and sometimes not."

Such descriptions indicate that these observers recognized two methods by which a pulmonary cavity could heal; the cavity might become lined by a natural membrane, or the diseased area might be replaced by fibrous scar tissue.

Modern authors have also provided accounts of these modes of healing, although, compared with the abundance of clinical observations, full anatomic proof is surprisingly infrequent. Epithelialization and dense fibrosis of the cavity wall, following substitution of the local active tuberculosis by ordinary granulation tissue has been described by Pagel⁷ (1932), Alexander¹ (1935), and Pagel and Robinson⁹ (1936). The replacement of a cavity by a fibrous scar has been demonstrated by Sweany¹¹ (1935). In their patients the course of the lesions was traced radiologically and the healing demonstrated anatomically. Pinner¹⁰ and, more recently, Marienfeld⁶ (1938) aptly review the clinical and anatomic literature of this subject.

Can a cavity heal in any other way? We know that caseous lesions become inspissated and shrunken and that calcium salts commonly are deposited in these areas, and the radiologic appearances of such a quiescent lesion are familiar. Calcified foci at the site of a previously demonstrated excavation are sometimes mentioned in the literature, their development having been traced in serial skiagrams. Such a course was probably followed by the following illustrative case:

CASE 1.—M. M., female, aged 34. Artificial pneumothorax was induced in June, 1931, when all zones of the right lung were involved. A definite cavity in the lung was reported and sketched several times. No calcification noted (film not available). Sputum 1 ounce daily, and tubercle bacilli present. Six weeks later expectoration had ceased; 4 months later pleural effusion followed the spontaneous rupture of an axillary adhesion. Complete apical collapse persisted and the displacement of the mediastinum to the left concealed the upper in the mediastinal shadow. With gradual obliteration of the pleural space, the upper lobe again became visible, and in 1938 an area of calcification is seen occupying the site of the former cavity (Fig. 1).

Proof of this process by postmortem section of the lung has been lacking up to the present, though Graeff³ (1935) has recorded one example in which a cavity was filled by a homogeneous caseous mass which also obstructed the stem bronchus. Surrounding layers consisted of cells in various stages of destruction, with nuclear debris, and finally a capsule of fibrous tissue and collapsed alveoli. In the example next to be described, a system of cavities repeatedly demonstrated by skiagrams were found at autopsy to be replaced in a similar manner by caseous foci in which considerable calcification had occurred, and the lumen of the corresponding bronchi was completely filled by caseo-calcareous material.

CASE 2.—L. F., female, aged 21, was found to be suffering from pulmonary tuberculosis in September, 1935. Left artificial pneumothorax was induced in November, 1935, and she remained at a sanatorium until August,

FIG. 6

FIG. 1



FIG. 10

FIG. 8

FIG. 7

FIG. 1, Case 1.—Calcification at site of former cavity. Fluid in pleural cavity.

FIG. 6, Case 2.—Survey of the left upper lobe. *a*, Caseous and calcareous foci at site of former cavities; *b*, artificial pneumothorax with broad adhesions.

FIG. 7, Case 2.—Histological survey of some of the old caseous and calcified nodules. *Bd*, *B*, occluded bronchi.

FIG. 8, Case 3.—Left upper lobe. Group of 3 bronchi filled with caseous material (arrow). Remains of ragged cavity below.

FIG. 10, Case 4.—Left lung. (See text.)

FIG. 2

FIG. 3

FIG. 4

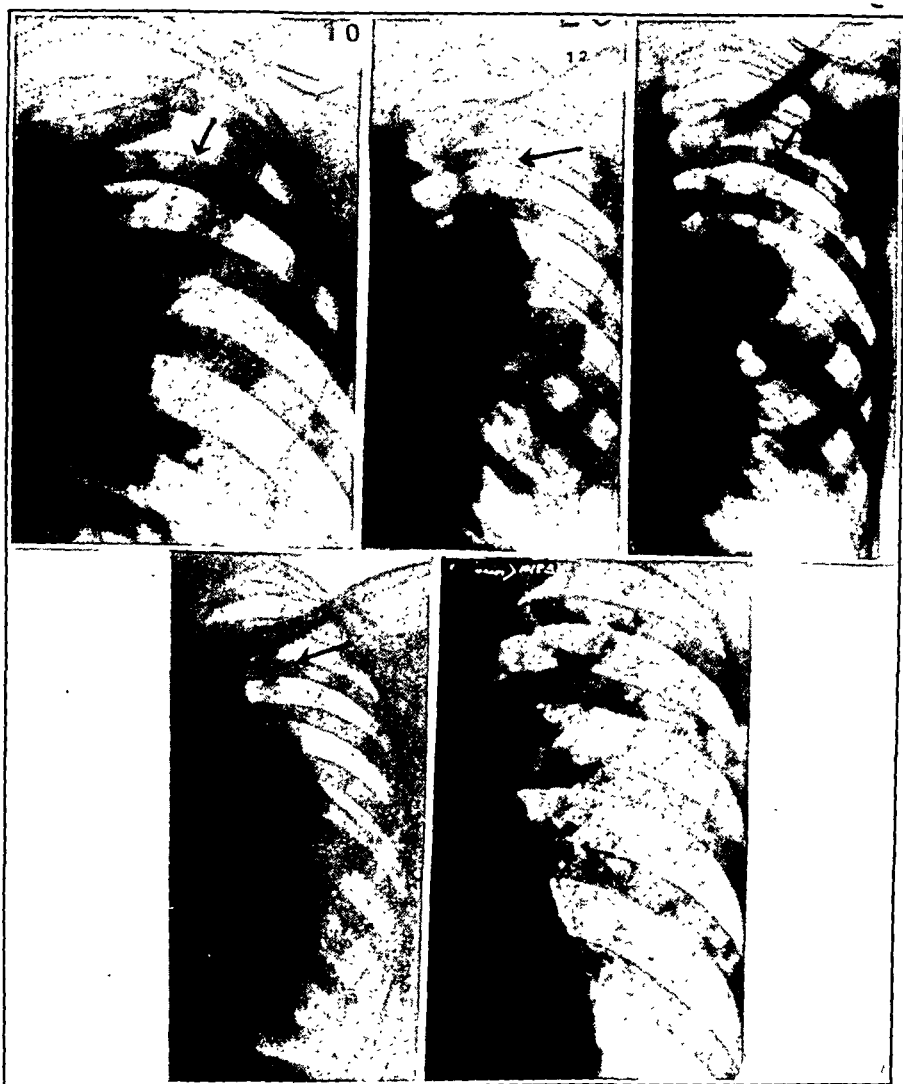


FIG. 5

FIG. 9

- FIG. 2, Case 2.—System of cavities in the left upper lobe, October, 1935.
 FIG. 3, Case 2.—Artificial pneumothorax. Cavity system still visible, December, 1935.
 FIG. 4, Case 2.—Similar picture, April, 1936.
 FIG. 5, Case 2.—Cavity system substituted by calcified nodules, December, 1937.
 FIG. 9, Case 4.—Left lung. Circular shadows (cavity system?).

1936. No evidence of disease in the right lung was then noted and the tubercle bacilli present in the scanty sputum disappeared after a few months, but Roentgen ray showed that the shadows indicating a system of cavities in the left upper lobe persisted, and pleural adhesions were present in this region. Temperature and pulse normal, blood sedimentation rate 34/42 (Westergren). While attending as an out-patient for refills evidence of disease became obvious in the right upper zone, and she was admitted to Clare Hall. Temperature 97 to 98°, pulse 80 to 90, sputum scanty, tubercle bacilli present. Blood sedimentation rate 63/96. Division of adhesions on the left side appeared too difficult and dangerous. A pneumothorax was induced on the right side. Temperature 97 to 98°, pulse 120, R. 26. Three weeks after induction, the patient died shortly after a severe attack of dyspnea.

Postmortem Examination. Subcutaneous emphysema was present on the right side of the chest, and on opening the thorax, emphysema of the anterior mediastinal tissues was seen. On the *right* side there was very marked collapse of the lung, and numerous fine string and veil-like adhesions were found.

On the *left* side the lower half of the pleural cavity was obliterated, and stretching across the pneumothorax cavity from the upper lobe a broad band of tissue (1 inch diameter) was attached to the axillary region of the chest wall. No lesions were found in other organs.

After hardening in formalin, section of the *right* lung showed caseous lesions, in a few of which were small central areas of liquefaction, but no older cavities. Close to the apex there were a number of emphysematous bullae (probably the fatal spontaneous pneumothorax and emphysema was due to the rupture of one of these).

Coronal section of the *left* lung through the broad adhesion showed marked thickening of the pleura. The upper half of the lung contained several old caseous and calcifying foci, and (Fig. 6) in particular in the broad adhesion there was a larger area of this nature occupying the site of the cavities seen in the earlier Roentgen ray films (Figs. 2 to 5). On microscopic examination, the obsolescent and partly calcified nature of these lesions was confirmed, and further it was clear that the bronchi to these areas were occluded by shrinkage and filling with caseous and calcifying material (Fig. 7).

Coryllos² (1933) and others have stressed the importance of obliteration of the bronchial lumen in the clinical healing of cavities. Kinking of the bronchus is suggested as the commonest cause, especially when some form of collapse therapy has been employed. Other factors must also be considered, and these include edema of the wall, tuberculous granulation tissue, fibrous stenosis and obstruction by a plug of caseous material. The last was probably the cause in the second case we have described; obliteration and obsolescence of the associated cavity, with the deposition of calcareous material in the inspissated cavity contents was the result.

The same process at an earlier stage is seen in the following case, where the findings resemble those described by Graeff, and illustrate again the changes which occur after closure of the draining bronchus.

CASE 3.—Q. A., female, aged 17, 8 weeks after the operation of extra-pleural pneumolysis (pneumothorax), developed an empyema of the extra-pleural cavity, following rupture of a tuberculous cavity in the lung at the time of operation. The tear was repaired by oversewing. She died 4

months after the operation from secondary hemorrhage. At post-mortem examination the remnants of the cavity were found, and the tributary bronchi were blocked by caseous and mucoid material (Fig. 8). The lumen of the cavity was filled with an inspissated caseous mass rich in cholesterol crystals and lime salts. This drying-up of the caseous contents suggests that the earlier stages of healing had occurred, and were dependent on the closure of the draining bronchi. But there were, in this case, several lobular pneumonic foci in the neighboring lung tissue, the result of aspiration of infective material.

The clinical diagnosis of cavitation, though greatly advanced by radiologic methods, is beset by pitfalls. When disease of the bronchi or pleural fistula can be excluded, the expectoration of $\frac{1}{2}$ ounce or more of sputum is strong indication of excavation in the lung, though cavities which provide no other clinical evidence owing to their very small size may, of course, yield mere traces of tuberculous expectoration. Ring-shaped shadows in the radiograph are also of obvious importance, especially with definite amounts of sputum, but caution should still be observed unless at some time a fluid level is seen in the suspected area. When an area of lung tissue has undergone an acute infiltration, a zone of leukocytic "precavernous demarcation" is found, which may show on a film as a nearly circular outline (Alexander, 1935). Should the process progress to caseation and the caseous material later be expectorated, this zone would become the granulating wall of a freshly formed cavity. Were such an area sectioned postmortem, it might superficially resemble the condition we have described above. Nevertheless, excavation has not yet occurred, and with due care it should not be confused with a healing cavity. The acute character of the process, the still-evident lung structure, the absence of calcification and of bronchial obstruction are important differences.

A different condition but perhaps not without affinity to this state of "precavernous demarcation" was seen in the following case, where the appearances on the radiograph had suggested a diagnosis of cavitation in the left upper zone.

CASE 4.—F. B., male, aged 27, was a contact of his father, who had fibro-cavernous phthisis. He was ill for a few months with lassitude, slight cough and scanty sputum, which contained tubercle bacilli, later proved by culture to be of the human type. In February, 1938, temp. 98 to 100°; pulse 90 to 120; blood sedimentation rate (Westergren) 40/73, and Roentgen ray showed infiltration in the right upper zone, and in all zones of the left lung, where the appearances also suggested cavitation in the upper zone (Fig. 9). Artificial pneumothorax was induced, but failed to produce improvement. A severe enteritis set in, and caused death 2 months later.

Post-mortem examination revealed the extensive and very acute tuberculous enteritis, with gangrenous ulcers, which was the immediate cause of death.

Lungs. In the left upper lobe there are three caseous areas the size of a large walnut including the bronchi leading to the apex and the subapical parts (Fig. 10). The caseous substance is soft and faintly red. In the dorsal portion there is some old caseous tissue gray in color and of harder

consistency. The lung tissue surrounding the foci is atelectatic. In the apex of the lower lobe, which appears to be dislocated mesially and vertically there is an area the size of a small tomato consisting of the same soft caseous and reddish mass as the described lesions in the upper lobe. The bronchus leading to the focus is filled with the same mass. There are a number of smaller foci of the same kind throughout the lower lobe.

Histologic Examination. The foci in the upper and in the apex of the lower lobe are caseous areas in a state of wholesale liquefaction. Between the liquefied parts, however, are areas of still preserved caseous tissue with some remnants of elastic fibers and just recognizable alveolar structure. The remains of caseous tissue are surrounded by edematous fluid interspersed with innumerable leukocytes. Towards the thick fibrotic capsule of the foci the mass is more solidly caseous and contains patches of red blood cells and small vessels engorged with erythrocytes. The surrounding lung tissue is atelectatic, but not infiltrated.

Here there were a number of caseous lesions in a state of liquefaction. Because of the presence of red blood cells, especially in the central parts, this may be called "red liquefaction," which is due to a high degree of toxic and hypersensitive irritation of the vessels, described by Pagel and McCallum⁸ (1935).

The histologic picture rules out the possibility that the foci were originally cavities filled by a blood clot, now changed in color by the breaking down of the red cells. It might have been expected that the lesions described would have caused some solid focal shadows in the radiograph. Two explanations suggest themselves. The first is that at the time of the film, a state of "precavernous demarcation" was present, and that the collapse by pneumothorax stimulated the production of a fibrous wall around the liquefying foci. Coryllos stresses the importance of pneumothorax in limiting the oxygen supply of the lung tissue and so stimulating fibrosis. But the areas under consideration showed a decreased density rather than an opacity to Roentgen rays. It is most probable therefore that cavities were present having very thick caseous walls, and that pneumothorax by kinking and blocking the bronchi, led to absorption of the contained air and approximation of the walls, so forming a solid caseous mass which began to liquefy.

The processes at work in the last 2 cases of this series therefore throw some light on the method of healing by calcification demonstrated in the second case.

Summary. The healing of active cavitation may follow one of three markedly different courses, namely:

(a) The ingrowth of an epithelial lining after the tuberculous disease has been replaced by ordinary granulation tissue and fibrosis.

(b) Approximation of the walls with the formation of a fistulous tract or of a strand of fibrous tissue if closure is complete, and

(c) Filling of the cavity with caseous material in which progressive calcification occurs.

Histologic and radiologic evidence is produced which is in agreement with this suggestion.

Such radically differing methods in the healing of cavities may be due to some difference in the origin and mode of formation of such lesions.

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THE ANTIANEMIC EFFECT OF YEAST IN PERNICIOUS ANEMIA.*

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It has been the generally accepted opinion that "autolyzed" yeast possesses a factor which, after mixture with the gastric secretion of normal persons, produces a hematopoietic response when fed to patients suffering from pernicious anemia. According to this view, unless normal gastric juice is added, such an effect does not occur. This "extrinsic" or dietary factor, furthermore, is thought to be lacking in non-autolyzed yeast.

This report described the effects of the administration of non-autolyzed yeast to 23 patients suffering from pernicious anemia.† The study was commenced when it was found that animals, given a diet supposedly lacking in "extrinsic factor"²⁷ failed to develop macrocytic anemia. Each of the constituents of this diet, which included brewers' yeast, was consequently tested for antianemic value. When this yeast, administered to a case of pernicious anemia in amounts corresponding to those given the animals, was followed by a well-marked hematopoietic effect, experiments were carried out with the purpose of answering the following questions: How regularly will the oral administration of yeast cause a hematopoietic

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† A preliminary report of these studies was presented at the meeting of the American Society for Clinical Investigation, in Atlantic City, May 2, 1938 (Abstract in *J. Clin. Invest.*, 17, 501, 1938).

response in cases of pernicious anemia? Will preliminary mixture of yeast with normal gastric secretion produce a substance which has greater antianemic value than yeast alone? Does the anti-anemic effect of yeast depend on persistence of intrinsic factor in the gastric secretion of the patient? What is the nature of the yeast substance and what is its relation to the antianemic principle contained in liver? The following experiments were carried out with the object of answering these questions.

Review of Literature. Interest in the antianemic value of yeast was originally aroused by certain points of similarity between the water-soluble vitamins and the antianemic principle^{8,10a} or its precursor, the "extrinsic factor,"²³ as well as by Wills' description²⁶ of a type of macrocytic anemia in India which she considered to be due to a vitamin deficiency. This tropical anemia, she found, could be treated effectively by marmite, an autolyzed yeast concentrate.

Probably because of Wills' experience, in the trials which were made in cases of pernicious anemia, autolyzed yeast ("marmite," "Vegex") received almost exclusive attention and very few studies were made of the anti-anemic value of non-autolyzed yeast or of extracts which could be given parenterally. The reports concerning the value of autolyzed yeast were by no means in agreement. Goodall¹² found marmite in doses of 45 to 150 gm. definitely effective when fed in 3 cases of pernicious anemia and recorded less convincing data regarding a number of other cases. Ungley^{24,25} also observed good hematopoietic responses in several cases and an alcohol extract of marmite, given daily in amounts derived from 120 gm. produced a good response in 2 cases. Connery and Goldwater⁹ concluded that Vegex (6 to 24 gm. daily) may excite a reticulocyte response in cases of pernicious anemia, but the increases they record are small.

Using small amounts (12 gm. daily), Strauss and Castle²³ found Vegex and an alcohol extract of this substance ineffective when given alone, but a well-marked hematopoietic response followed preliminary incubation with gastric juice. The experience of Groen¹³ who used 24 to 36 gm. of marmite daily was the same, whereas the Lassens¹⁷ found their autolyzed brewers' yeast (12 to 20 gm. daily) ineffective even after incubation with gastric juice.

Davidson found marmite of no value whatever in 3 of his first 4 cases^{10a} and only in 2 out of 12 additional cases reported later^{10b} did a satisfactory hematopoietic effect result (34 to 90 gm. were used daily). It is noteworthy in considering Davidson's failure to demonstrate antianemic value in marmite in 13 cases, that in 2 of these cases a response to liver had already occurred, in 4 treatment by the use of liver was also not followed by the customary response, and in 3 cases the ineffectiveness of marmite by mouth was compared with the value of liver administered parenterally. Only in 4 of the cases in which marmite had failed was it shown that liver by mouth was effective.

As already mentioned, non-autolyzed yeast has received little trial in the treatment of pernicious anemia. Cohn, Minot, Alles and Salter⁸ stated, in 1928, that no response was obtained in 1 patient given 120 gm. of yeast cake daily for 8 days, nor were 51 gm. of a yeast extract effective in another case. Slight improvement followed the administration of 10 gm. daily of a vitamin extract derived from yeast together with 90 cc. of an extract of wheat embryo. Ungley²⁴ used dried yeast (Yestamin) in 1 case only. The response was poor, but neither was marmite nor liver followed by an adequate response.

Russell²¹ gave dried brewers' yeast (Harris) (about 12 to 24 gm. daily) to 4 patients. In 2 a moderate reticulocytosis followed, but the increases subsequent to the injection of liver extract were more than twice as great. In the remaining 2 cases, the reticulocyte change associated with the ingestion of yeast was insignificant, although in 1 of these patients the erythrocyte count increased nevertheless.

Spies, Payne and Chinn²² gave 3 patients suffering from pernicious anemia an incubated mixture of normal gastric juice and 50 gm. autoclaved brewers' yeast (Harris) daily for 10 days. Two other patients were given the same amount of yeast after incubation with pepsin and trypsin instead of gastric juice. No change in the blood of any of these 5 patients occurred. This treatment was followed by the intramuscular administration of liver extract, which produced a characteristic response.

Ungley reported^{24,25} that alcohol extracts of fresh yeast caused definite although moderate reticulocyte responses in 3 cases of pernicious anemia and in 1 instance a marked reticulocytosis occurred. In each of these cases, the subsequent oral administration of liver extract was followed by a greater effect than had been produced by the yeast extracts. In another patient an extract of yeast made by a method used in liver extraction caused only a slightly response. This patient, however, did not respond readily to liver by mouth.

It is of interest that in 1 of Ungley's cases above mentioned, an extract of autolyzed yeast was no more effective than that derived from fresh yeast. On the other hand, in another patient, an alcohol extract of marmite caused a well-marked reticulocytosis whereas "vitamin B₂ concentrates" derived from an aqueous extract of fresh yeast, produced less marked reticulocytosis.

Aqueous as well as alcohol extracts of 60 to 70 gm. of yeast were inactive, even after incubation with gastric juice, in 4 cases reported by Groen.¹³ Lassen and Lassen¹⁷ noted a very slight response in 2 out of 3 cases treated with a yeast extract which had been incubated with normal gastric juice.

Only Ungley²⁵ has reported on the use of yeast preparations parenterally. An alcohol extract derived from 27 to 48 gm. fresh yeast was given daily to 2 patients, a lead acetate fraction to 1, and an extract made by a method used for liver extraction to another. The last extract, given in amounts derived from 100 gm. daily, caused a very slight increase in reticulocytes and the erythrocyte count did not change. This patient, it may be noted, improved only slowly on liver therapy. The other extracts above mentioned caused no change in the blood when they were given parenterally although, as already mentioned, they had some beneficial effect when given by mouth.

In summary, a survey of the literature indicates that autolyzed yeast has been shown to have been effective in causing a hematopoietic response in about one-third of the cases of pernicious anemia in which it was tested, when amounts of 45 gm. or more were used daily. Several investigators have shown that smaller quantities are effective after incubation with gastric juice. As regards non-autolyzed yeast, it seems to have been tacitly assumed that it does not possess antianemic potency. Actually, however, trials have been reported in a few cases only, and in a number of those in which such treatment failed, the test was not altogether satisfactory or the amounts used were small. An important oversight in many of the experimental studies reviewed, is the failure to determine, when yeast was ineffective in causing a hematopoietic response.

whether liver or liver extracts, likewise given *by mouth*, were effective. Very often parenteral therapy was resorted to and the possibility of failure of absorption through the gastro-intestinal tract was completely ignored. The equivocal results following the use of extracts of yeast are inconclusive, for to assume that an extract is necessarily representative of the yeast as a whole is not justified.

Material and Methods. These observations have been made in patients whose clinical history and physical and laboratory findings fulfilled all the usual criteria required for the diagnosis of classical pernicious anemia. Achlorhydria, even following the injection of histamine, was present in each. All patients studied on the wards of the hospital were given a diet free of liver, kidney, brain and meat and in the majority the diet also lacked eggs. Except in the 1 instance which will be mentioned, as far as we were able to ascertain, the diet of these patients before coming to the hospital, had not been deficient. The observations have been summarized in Table 1 and are illustrated in the various figures. In the descriptions of the cases, only complicating diseases are mentioned. Details regarding history and physical findings are omitted for the sake of brevity.

The patients studied in the dispensary were asked to take no liver or other food or medication which is known to cause hematopoiesis in cases of pernicious anemia. It is believed that they adhered to these instructions.

It should be pointed out that all cases of pernicious anemia available for study were used as they appeared, *no selection of favorable cases* being made.

Three brands of yeast have been used: 2 of these (N, M) are known as "brewers'" yeast, while 1 is a "bakers'" yeast (F). Except in the one instance so indicated (M[w]), the yeast was in the form of a dry powder sold for nutritional purposes. In such powders the yeast cells are dead.

Yeast "N" is derived from a strain of *Saccharomyces cerevisiæ* and is grown on a carefully selected medium free of meat, kidney, stomach, liver or egg preparations of any kind. Autolysis is not allowed to occur. Nothing is added to the yeast powder. This yeast is said to contain about 12 to 13 international units of B₁ and 13 Sherman and Borquin units of "G" per gram. The "protein" content ($N \times 6.25$) is 45.3%.

Yeast "M" has been accepted by the Committee on Foods of the American Medical Association.¹ "The yeast is cultivated by inoculating a sterilized wort containing dextrose, sucrose and raffinose of molasses and other vegetable products and nutriments of organic and inorganic origin, with a pure culture of *Saccharomyces carlsbergensis*." The fermentation is carried on in a filtered air atmosphere and is much slower than for aerated bakers' yeast. The yeast is centrifuged and washed several times and then it is spray dried. The temperature attained by the yeast in the process of drying is less than 100° C. and probably not more than 70° C., and the heating time is probably less than 30 seconds. The protein content is 48%; carbohydrate, 39%. Each gram is said to contain at least 25 international units of B₁ and 42 Sherman units of G.

The above yeast was also obtained before drying as a filtered wet yeast (Mw) and in this form was given to 1 patient (M. Th.).

The bakers' type yeast (F) used in these studies is grown in a molasses and grain wort. It is a strain of *Saccharomyces cerevisiæ* grown rapidly at a higher temperature than the brewers' yeast. It is dried on a drum drier. It is said to contain approximately 160 international units of B₁ and 20 to 25 Sherman units of G per gm. of dry yeast. The protein content is 49.5%, carbohydrate about 29%.

Various extracts of these yeast powders were made for oral and parenteral use. One, "Yeast Ext. al.," was a 65% alcohol extract as described by

Ungley.²⁴ It was so diluted that 1 cc. of extract represented 1 gm. of yeast. Yeast extract "P.D." was prepared from yeast N by making a thick paste with water, freezing this and subsequently suspending the frozen mass in water. This was allowed to stand about 18 hours, the solids were then removed by centrifugation and the liquid dried in a vacuum drier at a temperature of 150° F. or less. The dried material was milled. The weight of the extract was 11.25% of that of the original quantity of yeast used.

Yeast extracts for intramuscular injection were made by 2 different methods. Extracts Y₁, Y₂ and Y₃ were made in the same way as liver extract is made, the main steps of the procedure being digestion of the yeast with N/5 sulphuric acid, extraction with water at a temperature of 85° C., concentration *in vacuo*, precipitation with alcohol (70%) and finally solution of the precipitate in water. Extract YL was made according to the insulin process in which preliminary extraction is made by means of an acid-alcohol solvent rather than with acid and water.

The "double" reticulocyte method for assaying antianemic substances in cases of pernicious anemia was used.¹⁹ After a preliminary period of observation on a diet containing no recognized antianemic factors, the substances to be tested were given daily in successive periods of about 10 days' duration, a substance expected to produce no or little effect being given first and the (probably) more potent substance being given next. If the second substance is more potent than the first an increase in reticulocytes will occur, even though the first has already caused reticulocytosis. The magnitude of the second reticulocytosis as compared with the first and the effect on the number of red corpuscles, indicate the relative potencies of the two substances. If the first substance has already produced a maximal effect, no secondary reticulocyte rise will occur. By giving a number of different test substances in suitable order, comparison can be made in the same patient of the effectiveness of a variety of antianemic agents.

In some of the patients, for various reasons concerned with the health or pleasure of the patients, the test periods were not as long as theoretical considerations would have made desirable. In a few, the preliminary period of observation before test substances were given, was short. In others, administration of the substances assayed was unavoidably irregular. Again, in some cases it was not possible to compare the effectiveness of yeast given by mouth with that of liver given by the same route. Finally, in several patients, the presence of complications inhibited their response.

LEGEND FOR TABLE 1.

The table should be read from left to right. In most of the patients there were only 3 periods of assay. When there were more than this number of periods, the 4th, 5th and 6th will be found below the first three, and the 7th, 8th and 9th under the second three.

In the "Day of peak" column, the day given is that on which the highest reticulocyte count which followed administration of the substance assayed, was found. The number in parentheses indicates the total number of days of observation up to the time of this reticulocyte count.

Legends: "i.m." refers to intramuscular administration; "G. J." refers to normal gastric juice; "Y. E." to yeast extract; "L. E." to liver extract; "B. M." to beef muscle; "D. H. St." to desiccated hogs' stomach.

Full details regarding the various kinds of yeast and the yeast extracts are given under "Material and Methods."

Liver Extract "343" is the powdered liver extract for oral use manufactured by Eli Lilly & Co.; Liver Extract "L" is the extract (unconcentrated) of the same manufacturers for parenteral use. Liver Extract "W" is that marketed as Campolon by the Winthrop Chemical Company. Liver Extract "Le" is that made by Lederle, Inc. Liver Extract "J.H.H." is an extract made by ourselves from Lilly Liver Extract 343 and prepared for parenteral use. Full details are given in the individual case histories.

TABLE I.—SUMMARY OF RESULTS OF ASSAYS IN CASES OF PERNICIOUS ANEMIA.

				Period One.						Period Two.						Period Three.														
Patient.	Age.	Sex.	Weight, kg.	Substance assayed.	Amt., gm. or cc.	Route.	No. of days.	R. B. C.s.			Reticc., %.	Day of peak.	Substance assayed.	Amt., gm. or cc.	Route.	No. of days.	R. B. C.s.			Reticc., %.	Day of peak.	Substance assayed.	Amt., gm. or cc.	Route.	No. of days.	R. B. C.s.			Reticc., %.	Day of peak.
								Initial.	At end of period.	Highest.							Initial.	At end of period.	Highest.							Initial.	At end of period.	Highest.		
C.B.	59	F	60	Yeast N	104	Oral	10	2.90	3.19	0.1	12.1	9th (13)	Yeast N	120	Oral	20	3.19	4.14	6.4	1.2	(44)	L. E. J.H.H.	3	i.m.	10	3.21	3.75	1.9	1.8	2d
E.R.	69	F	75	Yeast N	168	Oral	10	1.90	2.77	1.0	15.8	5th (16)	Yeast N + G.J.	150	Oral	11	2.77	3.15	6.0	4.1	(27)	Yeast N + G.J.	44	Oral	12	2.51	2.95	2.8	3.0	10th
B.A.	43	F	44	Yeast N	44	Oral	11	1.81	2.26	2.6	7.0	6th (26)	Yeast N + G.J.	150	Oral	10	2.26	2.51	3.0	5.8	(39)	Yeast N + G.J.	150	Oral	12	2.51	2.95	2.8	3.0	(54)
G.Y.	68	M	64	B. M.	200	Oral	14	1.30	1.33	1.2	2.4	5th (7)	Yeast N	96	Oral	48	1.33	4.16	1.4	27.3	(26)									
C.V.	60	M	70	B. M.	200	Oral	15	1.81	2.43	2.8	9.7	9th (12)	Yeast M	125	Oral	10	2.43	3.31	2.0	6.2	(25)									
S.B.	57	F	66	B. M. + FeSO ₄	200	Oral	14	1.86	1.75	0.2	2.2	12th (24)	Yeast F.	99	Oral	9	1.75	1.92	2.2	5.4	(34)	L. E. 343	24	Oral	6	1.02	2.32	3.6	3.8	5th (41)
Period 4				L. E. W.	10	i.m.	3	2.32	3.68	2.4	16.6	6th (48)																		
M.K.	45	M	80	B. M.	200	Oral	7	1.97	2.08	0.4	2.8	4th (150)	Y. E. YL	4	i.m.	7	2.08	1.57	1.2	2.4	(156)	Y. E. P.D.	64	Oral	8	1.57	1.81	2.0	6.6	7th (168)
Periods 4, 5 & 6				Yeast N	115	Oral	8	1.81	1.74	6.4	6.6	8th (177)	L. E. 343	12	Oral	10	1.54	1.86	6.6	6.6	(181)	L. E. W.	5	i.m.	10	1.86	3.12	2.6	23.4	5th (192)
J.M.	67	M	52	B. M.	200	Oral	10	1.91	1.91	0.8	2.0	8th (14)	Yeast M	26	Oral	9	1.91	1.89	0.8	1.6	(68)	Y. E. Y ₃	3	i.m.	10	1.89	1.75	1.2	12.3	5th (36)
Periods 4, 5 & 6				Y. E. Y ₃	6	i.m.	8	1.75	1.90	0.6	5.4	12th (54)	Y. E. al.	77	Oral	20	1.90	2.14	1.8	4.2	(57)	Yeast F	81	Oral	5	2.14	2.37	1.2	1.8	4th (77)
Periods 7 & 8				L. E. 343	12	Oral	10	2.37	2.04	0.6	5.3	7th (86)	L. E. L.	3	i.m.	10	2.59	3.74	4.8	6.4	(98)									
L.D.	65	F	72	D. H. St.	19	Oral	14	1.04	1.22	4.4	15.3	7th (6)	Y. E. Y ₁	3	i.m.	2	1.30	1.11	4.0	9.4	(27)	Yeast M	72	Oral	40	1.05	4.07	2.9	19.6	7th (43)
M.Th.	38	F	50	Y. E. Y ₁ , Y ₂	3	i.m.	21	2.64	2.05	0.2	2.1	3d (38)	Yeast M(w)	80	Oral	10	2.05	2.00	1.4	2.4	(63)	Yeast M	50	Oral	10	1.78	1.90	0.8	4.2	7th (53)
Periods 4, 5 & 6				Yeast N	50	Oral	13	1.90	2.26	2.2	7.8	7th (65)	Yeast N	100	Oral	33	2.26	1.80	6.8	1.8	(79)	D. H. St.	30	Oral	49	1.80	3.49	1.0	14.2	8th (116)
M.T.	68	F	73	Y. E. P.D.	30	Oral	10	1.64	1.63	0.4	3.8	10th (17)	Yeast M	54	Oral	10	1.63	1.50	3.8	5.0	(22)	Yeast M	80	Oral	16	1.50	1.60	2.8	7.8	10th (37)
Periods 4 & 5				L. E. 343	12	Oral	10	1.40	1.52	5.8	9.2	5th (50)	L. E. W.	5	i.m.	10	1.52	2.07	1.6	11.4	(62)									
L.B.	46	F	50	Y. E. P.D.	17	Oral	10	1.04	1.03	7.4	5.1	15th (15)	Yeast F.	75	Oral	9	1.03	0.94	4.0	4.6	(36)	Yeast N	75	Oral	3	0.94	0.93	3.6	10.4	6th (33)
Periods 4, 5 & 6				L. E. 343	12	Oral	10	0.98	1.29	5.2	21.8	6th (42)	Y. E. YL	5	i.m.	10	1.29	1.22	5.4	6.0	(32)	L. E. L	5	i.m.	10	1.22	2.40	2.2	14.6	7th (67)
L.E.S.	72	M	60	Yeast F	90	Oral	10	1.16	0.93	0.8	1.6	10th (18)	Yeast M	90	Oral	21	0.93	1.58	1.6	13.4	(27)	L. E. Le	1.2	i.m.	11	1.58	2.34	3.0	13.3	6th (45)
J.Mc.	61	M	60	Yeast F	90	Oral	21	3.40	3.57	0.4	4.6	20th (26)	L. E. 343	12	Oral	9	3.57	3.22	4.4	6.2	(34)									
E.G.	58	M	55	Y. E. Y ₂	5.4	i.m.	10	2.18	1.66	0.8	0.8	6th (48)	Y. E. al.	80	Oral	7	1.88	1.76	1.2	1.2	(59)	L. E. J.H.H.	2.3	i.m.	10	1.76	2.88	0.8	15.2	8th (69)
Periods 4, 5 & 6				Yeast F	84	Oral	10	3.31	2.77	0.4	4.4	7th (215)	Yeast M	126	Oral	21	2.77	2.87	2.6	2.2	(224)	L. E. 343	16	Oral	7	2.87	2.65	1.8	3.8	8th (234)
Periods 7 & 8				L. E. 343	24	Oral	9	2.65	2.81	2.4	3.2	5th (268)	Whole liver	230	Oral	12	2.81	3.48	2.4	1.2	(249)									

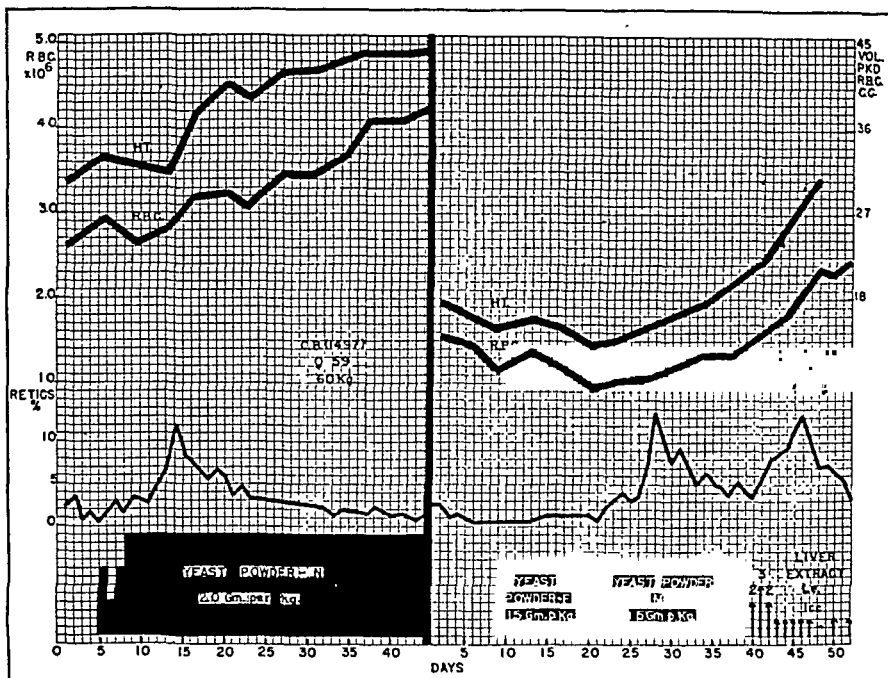


FIG. 1.—At the left, Patient C. B., showing hematopoietic effect of dehydrated brewers' yeast; at the right, Patient L. E. S., showing ineffectiveness of bakers' yeast. Ht refers to volume of packed red cells; R.B.C., to red cell count. In this and in the subsequent figures, these values are so plotted in relation to one another, that, when there is macrocytosis, the Ht value appears above that for R.B.C. and when the mean size of the red cells is normal the two lines coincide. Oral therapy is indicated by blocks, parenteral treatment by arrows.

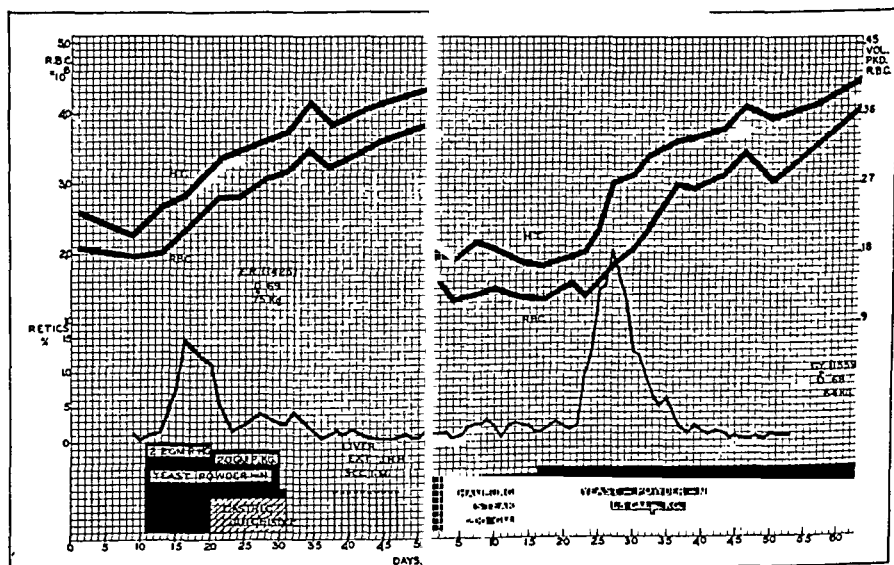


FIG. 2.—At the left, Patient E. R., showing maximal antianemic effect of brewer's yeast and the absence of a greater effect following administration of a mixture of this quantity of yeast with gastric juice from normal persons; at the right, Patient G. Y., showing lack of response to "extrinsic factor" (beef muscle), maximal response to brewers' yeast.

These defects in the clinical assays were unavoidable, but they are pointed out because they have a bearing on the interpretation of the results.

Results. *Dehydrated yeast powder caused rapid hematopoiesis in doses of 2 gm. per kg.* C. B. (No. 1497) (Fig. 1, left), 4 days after admission, was given brewers' yeast powder (N) in doses of 1.3 gm. per kg. body weight the first day, 0.7 gm. the second, 1.3 gm. the third, and 2 gm. per kg. in the succeeding 36 days. It was given in water as a drink, or as a paste on crackers. On the 9th day after treatment was commenced, and on the 6th day after full doses were used, the reticulocytes reached 12.1%. According to the statistics collected by Bethell and Goldhamer,³ the average expected maximum reticulocyte percentage following oral administration of

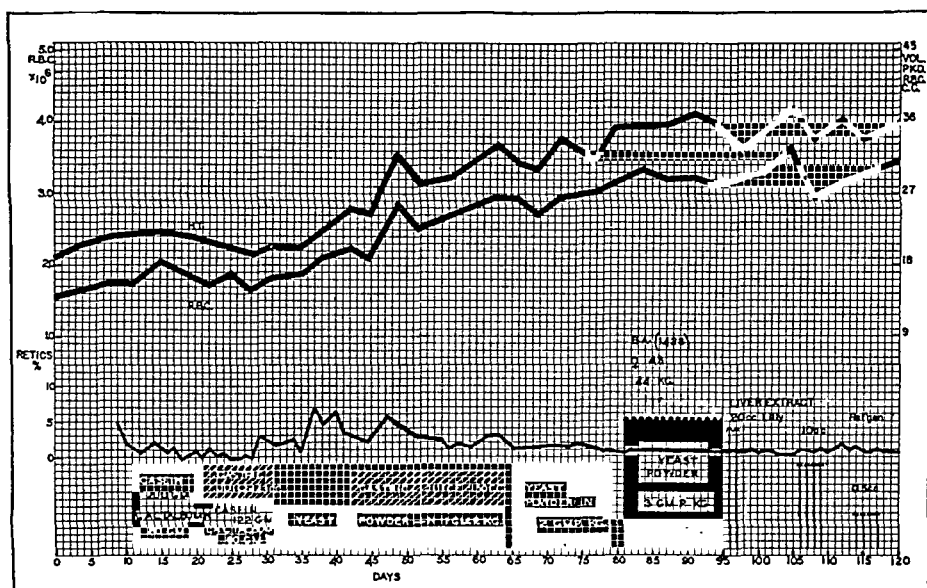


FIG. 3.—Patient B. A., showing submaximal response to a small quantity of brewers' yeast and additional effect of this quantity of yeast after mixture with normal gastric juice.

liver extract from 600 gm. of liver daily in this case was 4.9%. On the 10th day the erythrocyte count had increased from 2,620,000 to 3,190,000 and a level of 4,060,000 was reached 32 days after treatment was started.

Dehydrated brewers' yeast effective in causing well-marked reticulocytosis and red cell formation in doses of 2.2 gm. per kg. No well-defined additional effect produced by mixture with 150 cc. gastric juice. E. R. (No. 1425) (Fig. 2, left), had had recurring attacks of cystitis for 30 years; the blood-vessels were thickened. The catheterized urine contained numerous leukocytes. Urine culture showed a moderate growth of α streptococci.

Ten days after admission, dehydrated brewers' yeast powder (N) was given in doses averaging 2.2 gm. per kg. daily for 10 days. This was given in water as a drink, or as a paste on crackers. On the 5th day following, the reticulocytes had reached a level of 15.8%. The expected maximum increase in reticulocytes³ was 15.6%.

For the next 11 days, a slightly smaller quantity of yeast (2 gm. per kg.) was given together with 150 cc. of gastric juice. The gastric juice, obtained from normal fasting individuals following the injection of histamine, was neutralized just before mixing it with the yeast, and the whole mixture was promptly fed without incubation, as Castle and Ham recently advised.⁵

A slight secondary rise in the reticulocytes to a maximum of 4.1% on the 6th day followed. The erythrocytes continued to rise and 23 days after yeast therapy was commenced the count had increased from 1,900,000 to 3,470,000. During subsequent treatment with liver extracts parenterally (10 injections of 3 cc. each of liver extract made by ourselves, 1 cc. representing 5 gm. liver; 2 injections of liver extract, Lilly, unconcentrated, 10 cc. each), no further increase in reticulocytes occurred, and the erythrocytes gradually increased to 3,800,000 at the time of discharge.

After acid-washed casein and lactalbumin showed no antianemic potency even when given with gastric juice, yeast in doses of 1 gm. per kg. caused hematopoietic effect. Mixture of this quantity of yeast with gastric juice was followed by a secondary reticulocytosis. B. A. (No. 1428) (Fig. 3): blood pressure 164/90, marked dental caries. Casein and lactalbumin, acid-washed in our own laboratory, were given mixed with water, in amounts averaging 200 gm. of casein and 60 gm. of lactalbumin, daily for 10 days. No significant change in the blood occurred. These were then given in amounts averaging 122 gm. of casein and 35 gm. of lactalbumin, together with 143 cc. of normal gastric juice which had been neutralized just before mixing. On the 8th day, the reticulocytes rose to 3.4% but the erythrocytes did not increase in number.

The same yeast powder (N) which had been given patients C. B. and E. R. was next given in doses of 1 gm. per kg. daily for 11 days. On the 6th day following, the reticulocytes had reached a level of 7% and by the 10th day the erythrocyte count had risen from 1,810,000 to 2,260,000. The expected maximum increase in reticulocytes when extract from 600 gm. liver is given was 17.1%. In the succeeding periods of 10 and 12 days, the same quantity of yeast was given with 150 cc. of normal gastric juice daily, the two periods differing only in that the sources of the gastric juice were different. The gastric secretion was neutralized, mixed and fed in the manner already described.

On the 5th day following the administration of the yeast-gastric juice mixture, the reticulocytes had risen again to 5.8% and on the 10th day the erythrocyte count was 2,510,000. At the end of the 22 days during which this mixture was given, the erythrocyte count was 2,950,000.

During subsequent periods, as shown in Figure 3, yeast was given without gastric juice in amounts equivalent to 2 and 3 gm. per kg. daily. During the last period, probably not all the yeast given was consumed. No further reticulocyte increase occurred and, at the end of the period of yeast therapy, the erythrocyte count was 3,240,000. Liver extracts were then given intramuscularly (10 cc. of an extract made by ourselves daily for 8 doses, then 0.5 cc. Reticulogen (Lilly) daily for 4 doses), but on discharge, 24 days after injections of liver replaced yeast therapy, the erythrocyte count was only 3,420,000.

Administration of beef muscle ineffective; brewers' yeast in doses of 1.5 gm. per kg. caused maximal hematopoietic response; no further improvement on parenteral liver therapy. G. Y. (No. 1559) (Fig. 2, right); moderate arteriosclerosis. Two days after admission the patient was given 200 gm. beef muscle daily for 14 days. No reticulocytosis occurred and the erythrocyte count dropped slightly. The patient was next given dried brewers' yeast (N), 1.5 gm. per kg. daily, in divided doses mixed in water and flavored with chocolate, after meals. On the 10th day following the commencement of this treatment the reticulocytes reached a peak of 27.3% and the red cell count rose quickly, reaching 4,160,000 48 days after treatment was begun. The expected maximal reticulocyte percentage was 26%.

After 3 months of yeast therapy, this treatment was discontinued in order to see if parenteral liver treatment would bring further benefit. For 11 weeks Campolon (Winthrop), 10 cc. was given each week. No further increase in the blood count occurred.

In a patient whose diet had been inadequate, a hematopoietic response followed administration of beef muscle; a second response followed yeast therapy. C. V. (No. 1558) (Fig. 4, left), owing to his false teeth, had taken a diet poor in meat for the past 6 to 8 years, although he had eaten liver about once every 2 weeks. Commencing 3 days after admission, 200 gm. of beef muscle were given daily. On the 9th day following, the reticulocytes had increased to 9.7%. This was substantially less than a maximal response. The rise of the reticulocyte curve was gradual but its fall was precipitous. On the 4th day after the peak had appeared, the reticulocytes were 1.8%.

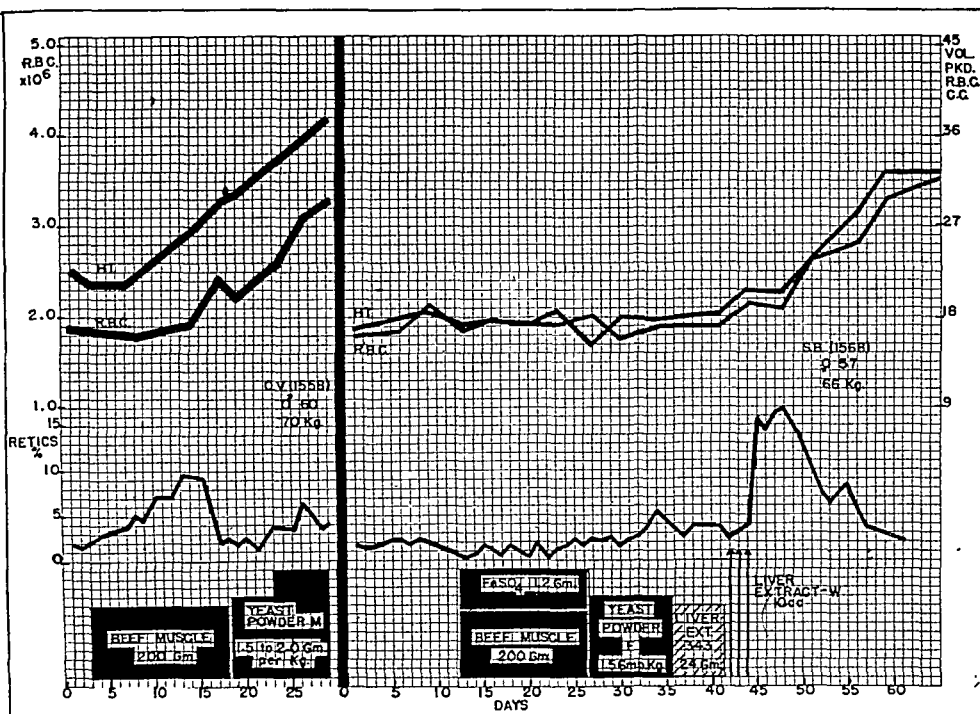


FIG. 4.—At the left, Patient C. V., showing hematopoietic response to “extrinsic factor” (beef muscle) and secondary response to brewers’ yeast; at the right, Patient S. B., showing ineffectiveness of oral therapy and maximal response to parenteral liver therapy. There was a slight reticulocyte rise when bakers’ yeast was given and no additional effect when large doses of liver extract were given by mouth.

The patient was next given brewers’ yeast powder (M), 1.5 gm. per kg. daily, mixed in water and taken after meals. This was continued for 4 days, when the dose was increased to 2 gm. per kg. daily, an amount which was taken for 6 days. On the 7th day following the commencement of yeast therapy, the reticulocytes had risen again to 6.2%. The expected maximum rise under oral liver therapy was 9%.

No response to beef muscle and iron, slight reticulocyte response to bakers’ yeast, no additional response to liver extract taken by mouth. Good hematopoietic response to liver parenterally. S. B. (No. 1568) (Fig. 4, right): markedly carious teeth. After a preliminary period of observation of 12 days, beef muscle, 200 gm., was given daily for 2 weeks, as well as ferrous sulphate, 1.2 gm. daily. The reticulocyte and red cell count remained unchanged. A bakers’ type yeast (F) was then given for 9 days in amounts corresponding to 1.5 gm. per kg. body weight daily. On the 7th day the reticulocytes had risen to 5.4% but the erythrocyte count increased very little. In a succeeding period of 6 days she was given liver extract (Lilly, 343), 24 gm. daily by mouth. The reticulocytes failed to rise. Liver extract (Compolon,

Winthrop) was then given intramuscularly in 3 doses of 10 cc. each. On the 6th day thereafter the reticulocytes had risen to 16.6% and the red cell count increased promptly.

In a case complicated by chronic bronchitis, sinusitis and emphysema, no response to beef muscle or to yeast extract given parenterally. Reticulocyte responses without increase in erythrocyte count, to a yeast extract, brewers' yeast and liver extract given orally. Good hematopoietic response to liver extract given parenterally. M. K. (No. 1557) (Fig. 5), a former coal miner, coughed frequently and expectorated a white, thick sputum occasionally

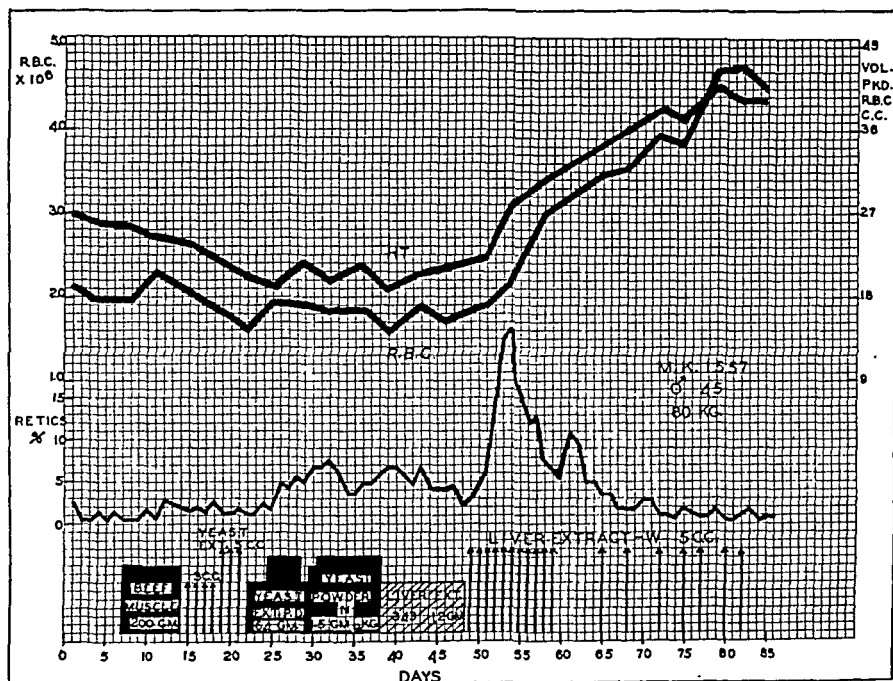


FIG. 5.—Patient M. K. (pernicious anemia complicated by chronic bronchitis and sinusitis), showing ineffectiveness of “extrinsic factor” (beef muscle) and of a yeast extract given parenterally, small reticulocyte responses of equal magnitude to an aqueous extract of brewers’ yeast, whole brewers’ yeast, and liver extract, all given by mouth, and maximal response to liver extract given parenterally.

streaked with blood. The chest was emphysematous and there were numerous râles at both lung bases extending as high as the scapula on the right side, which persisted after coughing. Roentgen ray of the lungs showed non-tuberculous infiltration of both roots.

After 8 days’ observation, 200 gm. beef muscle were fed daily for 7 days. No significant change in reticulocytes occurred. A yeast extract (YL) was next given intramuscularly, 3 cc. for 4 doses and 5 cc. for 3 doses. The blood count continued to drop. An extract of yeast (P.D. 915385) was then given in quantities corresponding to the amount derived from 7.4 gm. yeast per kg. body weight daily for 8 days. On the 7th day the reticulocyte count rose to 6.6%. In a succeeding period of 8 days, whole brewers’ yeast (N) was given in amounts corresponding to 1.5 gm. per kg. By the 8th day the reticulocytes had risen again to 6.6% but the erythrocyte count had still not increased.

Liver extract (Lilly, 343) was then given by mouth in 10 daily doses of

12 gm. each. After a slight drop, the reticulocytes reached a maximum of 6.6% on the 4th day of liver therapy. The erythrocyte count, however, remained essentially unchanged. Well-marked hematopoietic response occurred only after liver extract (Campolon, Winthrop) was given parenterally (5 cc. daily). On the 5th day the reticulocytes had increased to 23.4% and the red cell count rose promptly.

Ineffectiveness of beef muscle and of yeast in small doses given orally in a patient who had previously not responded to liver by mouth. Reticulocytosis following yeast extract given parenterally, followed by increase in number of erythrocytes. Slight reticulocytosis without increase in erythrocyte count following administration of liver extract by mouth. Submaximal reticulocytosis with prompt increase in red cell count following parenteral liver therapy.

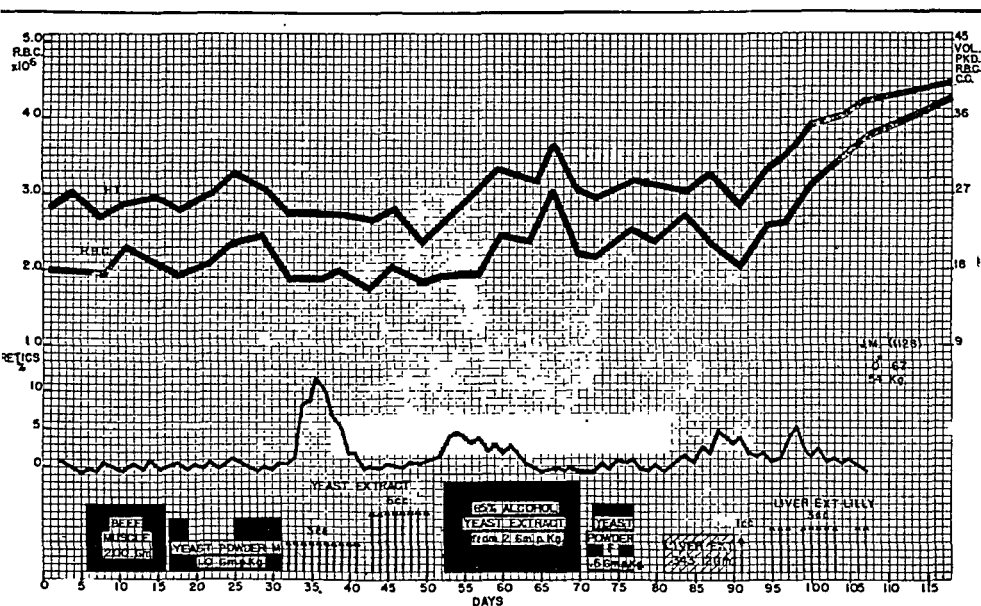


FIG. 6.—Patient J. M., showing reticulocytosis with some increase in the red cell count following parenteral yeast therapy in a patient who failed to respond adequately to yeast or liver extract given by mouth, and who subsequently responded to parenteral liver therapy.

J. M. (No. 1128) (Fig. 6): symptoms of angina pectoris and slight congestive failure, marked arteriosclerosis, blood pressure 150/80. On a previous admission he had failed to respond to "domestic liver extract,"⁷⁴ given by mouth, 600 cc. daily for 12 days, but responded to liver extract intramuscularly.

Five days after admission he was given 200 gm. beef muscle daily for 10 days. No change occurred in the blood. Brewers' yeast powder (M) was next given, 1 gm. per kg. daily. This was taken very poorly, however, there being considerable nausea and vomiting. Although the yeast was offered daily for 15 days, it is difficult to state how much was actually retained. Possibly this amounted, on the average, to one-half the quantity given. No reticulocytosis developed, and the erythrocyte count dropped slightly.

An extract of yeast (Y_3), made by a process used in manufacturing liver extract was given intramuscularly, 3 cc. daily for 10 days. Each cc. of this extract was derived from 5 gm. of yeast. On the 5th day following, the reticulocytes had risen to 12.3%. The erythrocyte count, however,

did not change. After a day's pause, the same extract was given in 8 doses of 6 cc. each. On the 3d day after the *last* injection of this extract the reticulocytes had increased again to 5.4% and following this the erythrocyte count rose, for the first time, from a previous level of 1,890,000 to 3,010,000 on the 19th day after the last injection. This increase in reticulocytes and in red corpuscles actually occurred while the patient was receiving a 65% alcohol extract of yeast, given in quantities corresponding to the amount derived from 2 gm. yeast per kg. body weight. The reticulocyte increase appeared on the second day of the alcohol extract period, however, and it would therefore seem that, if this was a specific response at all, it was more probably a response to the parenteral yeast therapy than to the alcohol

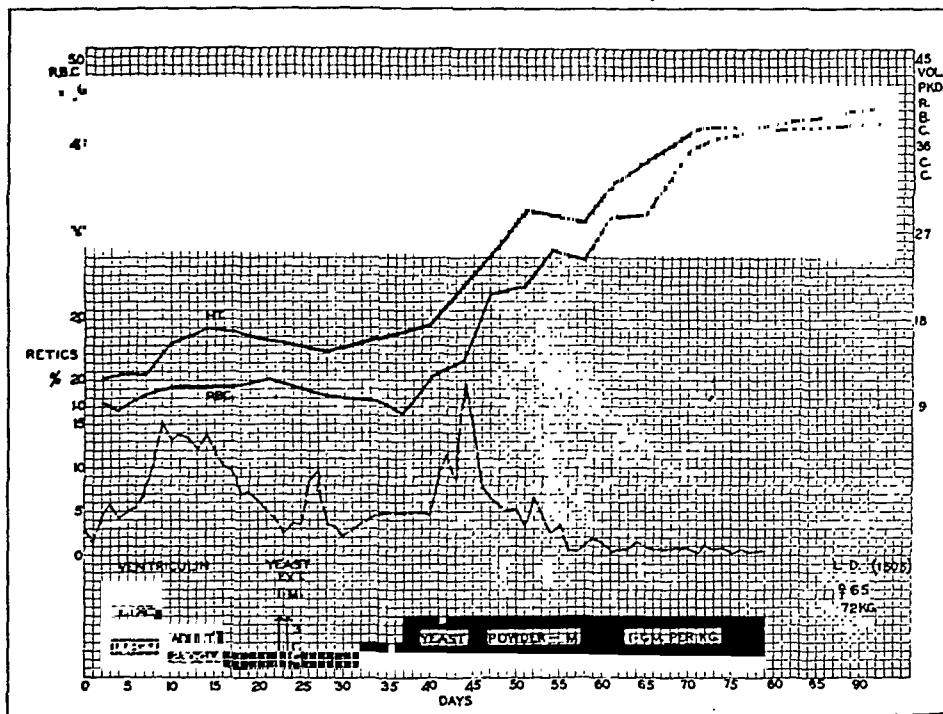


FIG. 7.—Patient L. D., showing reticulocytosis following 2 injections of yeast extract after a submaximal response had occurred to desiccated hogs' stomach. Subsequent prompt response to brewers' yeast given by mouth.

extract (Fig. 6). The ineffectiveness of the alcohol extract was indicated by the fact that the red cell count had dropped by the end of the period of administration of this extract.

The patient was next given bakers' yeast powder (F) in amounts equivalent to 1.5 gm. per kg. body weight. Nausea and vomiting developed and this treatment was therefore abandoned after 5 days. The blood did not change. During the next 10 days he received liver extract (Lilly, 343), 12 gm. daily. Reticulocytes increased to 5.3% on the 7th day but the number of red cells failed to increase. Finally, liver extract was given intramuscularly (Reticulogen, 0.5 cc. 1 dose, solution liver extract, Lilly (unconcentrated), 3 cc. daily for 10 doses). The rise in reticulocytes to 6.4% occurring on the 7th day was submaximal,¹⁶ but the red cell count rose to 4,250,000 4 weeks after parenteral liver therapy was started.

After responses to desiccated hogs' stomach, reticulocytosis again occurred following the administration of a small quantity of yeast intramuscularly, and rapid hematopoiesis followed the use of brewers' yeast powder in doses of 1 gm. per kg. This effect occurred in a patient with marked arteriosclerosis and latent syphilis. L. D. (No. 1505) (Fig. 7): generalized arteriosclerosis and arteriosclerotic heart disease, blood pressure 138/70, pyorrhea alveolaris, blood Wassermann and Kahn tests positive.*

This patient was first given ventriculin made from the stomachs of pig fetuses, 14.4 gm. daily for 7 days. On the 7th day following, the reticulocytes had risen to 15.3% and the erythrocyte values had also risen. In the succeeding period of 7 days she was given commercial ventriculin, made from the stomachs of adult pigs, 23 gm. daily. The reticulocytes failed to fall in the customary fashion but, on the 5th day following the first administration of commercial ventriculin the reticulocytes were 14%.

Treatment was discontinued for 5 days and on the 6th an extract of yeast (Y₁) made by a method that is used for making liver extract, was injected intramuscularly, 3 cc., on 2 successive days. Each cc. of this extract was derived from 5 gm. of yeast. The injection caused discomfort and had to be discontinued. Nevertheless, on the 5th day following the first injection the reticulocytes had risen to 9.4%. The erythrocyte count, however, did not rise.

Brewers' yeast powder (M) was next given, in doses of 1 gm. per kg. daily. For several days the amount consumed was uncertain because of nausea and lack of coöperation, but subsequently the yeast was taken regularly. Reticulocytes reached a peak of 19.6%. The erythrocyte values rose quickly and in 35 days the erythrocyte count increased from 920,000 to 4,070,000.

In a case in which a poor response to liver parenterally had occurred on a previous admission, yeast extract parenterally and "wet" yeast by mouth were ineffective, dried brewers' yeasts by mouth caused reticulocyte responses without sustained rise in erythrocyte count, and a submaximal hematopoietic response finally occurred when desiccated hogs' stomach was given. The red cell count of M. TH. (No. 567) on an earlier admission had been as low as 750,000. The anemia on that occasion responded satisfactorily to parenteral liver therapy, but, following a relapse due to discontinuation of a liver diet, the response to liver extracts of known potency given intramuscularly was poor and as the blood count rose the mean corpuscular volume fell below normal. Cessation of liver therapy and administration of iron, however, was followed by another relapse (R.B.C., 2,730,000; M.C.V., 98 c.μ.).

Yeast extract (Y₁) was given intramuscularly in 11 daily doses of 3 cc. each, without effect on the blood. Another extract (Y₂) in the same dosage was also ineffective. Whole brewers' yeast (Mw) which had not been desiccated, was given in doses equivalent to 1.5 gm. per kg. daily for 10 days. This caused no reticulocytosis. The same brand of yeast was then given as the dried powder, in doses of 1 gm. per kg. for 10 days. Reticulocytes increased to 4.2% on the 7th day. Another brand of brewers' yeast (N), taken in this dose for 13 days, was associated with a reticulocyte increase to 7.8% on the 12th day and for the first time the erythrocyte count began to rise. This effect did not persist, however, even though a larger quantity (2 gm. per kg.) was taken and ferrous sulphate was given as well. Desiccated hogs' stomach (ventriculin, Parke, Davis Company) was finally given, 30 gm. daily. Reticulocytes increased to 14.2% on the 8th day (expected percentage 22.2) and the erythrocyte count rose slowly from 1,800,000 to 3,490,000 7 weeks later.

* I am indebted to Dr. Robert Kirk and Dr. C. H. Kosmaler for permission to use this case.

In a hypertensive arteriosclerotic with urinary tract infection, an extract of yeast, whole brewers' yeast and liver extract given orally caused various degrees of reticulocytosis without increase in the red cell count. Submaximal hematopoietic response followed parenteral liver therapy. M. T. (No. 258) (Fig. 8) complained of precordial pain and was found to have arteriosclerosis, hypertension (blood pressure 214/110), cardiac enlargement, dental caries, hydro-nephrosis and chronic urinary tract infection.

After a week's preliminary observation, an extract of yeast (P.D. 913807) was given in quantities corresponding to the amount derived from 4 gm. of yeast per kg. body weight, for 10 days. On the 10th day a slight rise in the reticulocytes to 3.8% occurred. In the succeeding period of 10 days,

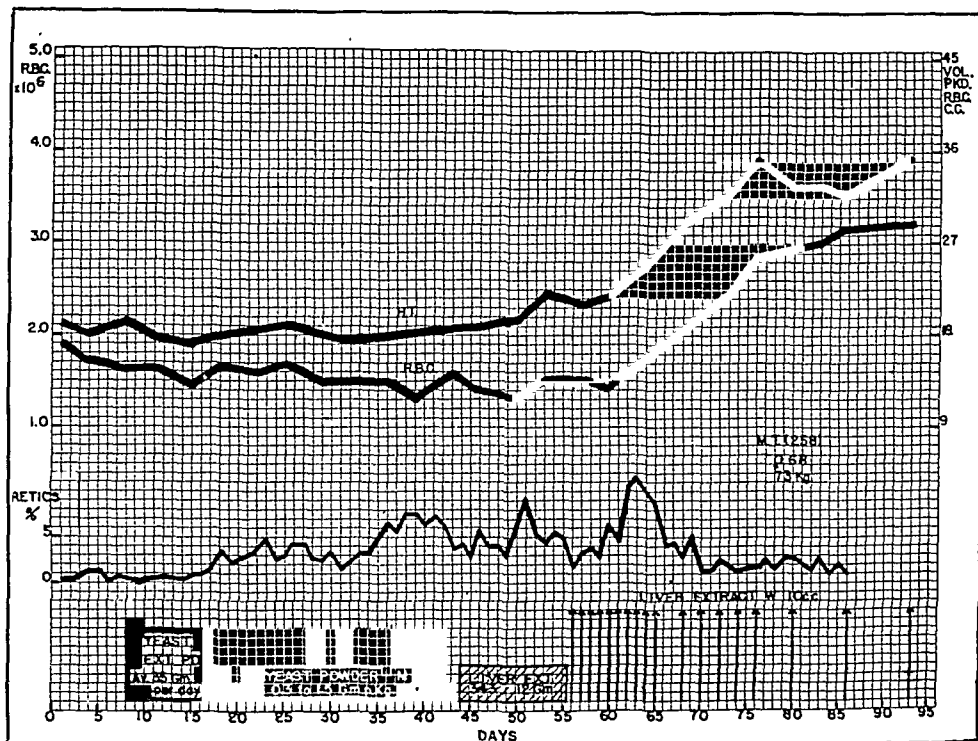


FIG. 8.—Patient M. T., showing failure of red cell count to rise in spite of reticulocytosis following oral therapy with yeast extract, whole brewers' yeast and liver extract; submaximal response to parenteral liver therapy.

whole brewers' yeast powder (M) in amounts corresponding to 0.7 gm. per kg. was given. Reticulocytes increased to 5% on the 5th day. During the next 16 days the same yeast was taken somewhat irregularly in amounts averaging about 1.1 gm. per kg. With this increased dosage the reticulocytes rose again, to a maximum of 7.8%. During all this time, however, no significant increase in the red cell count occurred.

In the succeeding period of 10 days, liver extract (Lilly 343) was given by mouth in doses of 12 gm. daily. On the 5th day, the reticulocytes reached a peak of 9.2% but the erythrocyte count still failed to rise. Finally, on intramuscular liver therapy (Campolon, Winthrop), 5 cc. daily, reticulocytes increased to 11.4% on the 7th day and for the first time the red cell count began to rise. The rise was slow, however, in spite of the fact that treatment of the urinary tract infection was instituted at this time.

No response to yeast extract or to bakers' yeast; slight response to brewers' yeast; more marked response to liver extract given by mouth. No response to

yeast extract given parenterally; good response to liver extract given parenterally. L. B. (No. 1609) (Fig. 9), after 7 days' observation during which time the reticulocytes rose as high as 10% although the red cell count did not increase, an extract of yeast (P.D. 913807) was given for 10 days in quantities corresponding to the amount derived from 3 gm. of yeast per kg. body weight. During this time the reticulocyte count decreased from the spontaneous rise of 10% to 2.4% on the 5th day after treatment with yeast extract was started, and only a slight upward turn to 5.1% occurred on the 8th day after the yeast extract was first given.

In the next period, a bakers' yeast powder (F) was given for 9 days in amounts equivalent to 1.5 gm. per kg. daily. No hematopoietic response

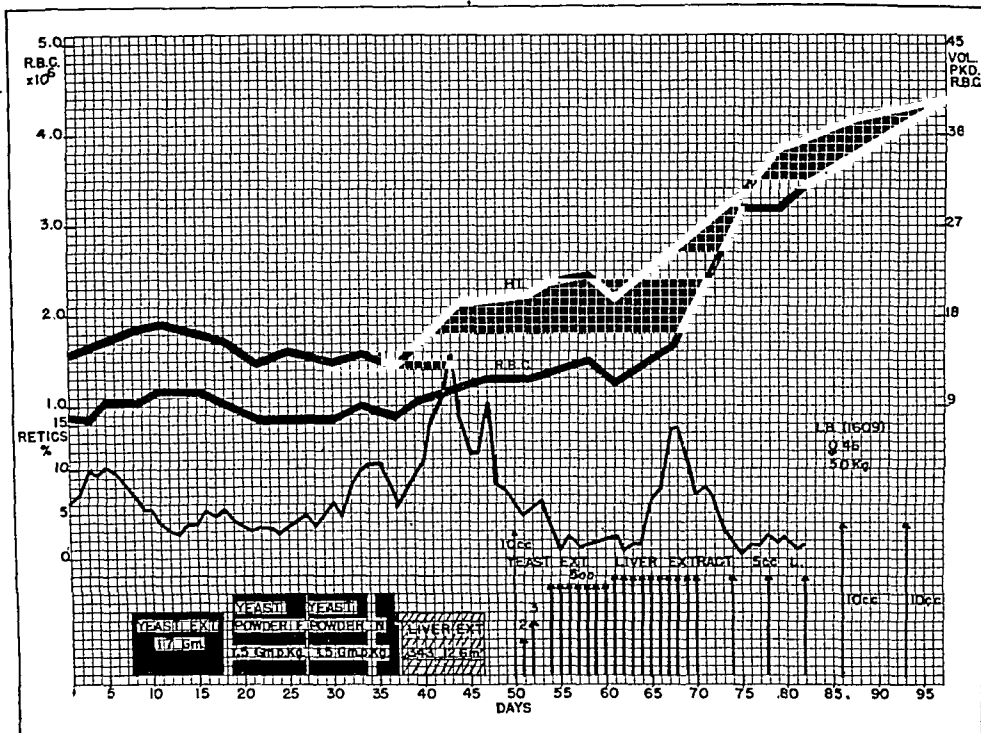


FIG. 9.—Patient L. B., showing ineffectiveness of a bakers' yeast, moderate hematopoietic effect of brewers' yeast and better response to liver extract, all given by mouth.

occurred. A brewers' yeast powder (N) was then given in similar amounts for 8 days. On the 6th day the reticulocytes had increased to 10.4%. Owing to the severity of the patient's anemia, yeast therapy was not continued, but instead liver extract (Lilly, 343), 12 gm. daily, was given orally for 10 days. On the 7th day of this period of treatment, the reticulocytes had risen to 21.8% and the erythrocyte count had begun to increase. The expected reticulocyte percentage³ was 35%.

After a pause of 3 days, an extract of yeast (YL) was given intramuscularly in doses averaging 5 cc. daily for 10 days. No increase in reticulocytes occurred, nor did the erythrocyte count rise. Following this, solution liver extract (Lilly, unconcentrated), 5 cc. daily, was given in 10 doses. Reticulocytes increased to 14.6% on the 7th day following and the erythrocyte count rose to 3,420,000 3 weeks after commencement of parenteral liver therapy.

No response to bakers' yeast, moderate response to brewers' yeast, secondary response to liver extract given parenterally. L. E. S.* (No. 1635) (Fig. 1, right), moderate arteriosclerosis, leukoderma. After a preliminary period of observation, a bakers' type of yeast (F) was given, in amounts equivalent to 1.5 gm. per kg. body weight daily for 10 days. The reticulocyte percentage failed to change and the red cell count dropped. For the next 20 days he was given brewers' yeast (M) in the same amounts. On the 9th day the reticulocytes had increased to 13.4% and at the end of this period a moderate increase in the red cell count had occurred. Liver extract (Lederle) was next given intramuscularly, 2 cc. daily for 3 days and 1 cc. daily for 5 doses thereafter. Reticulocytes increased to 13.3% on the 6th day and the erythrocyte count rose promptly.

Little change in blood after bakers' yeast or liver extract by mouth. Improvement following parenteral liver therapy. J. Mc. (No. 649), red blood cells 3,410,000, after 7 days' observation was given bakers' yeast, 1.5 gm. per kg. daily for 21 days. The highest level attained by the reticulocytes was 4.6% on the 18th day. By the end of the 21-day period the erythrocyte count had not risen although some symptomatic improvement had occurred.

Liver extract (Lilly, 343) was next given in 9 daily doses of 12 gm. each by mouth. On the 9th day the reticulocytes were 6.4% and the red cell count was 3,220,000. Further detailed observation was not possible but the patient received liver extract (Lilly) intramuscularly, in 2 doses of 20 and 10 cc. each, and 10 cc. each week for the next 4 weeks. Six weeks after intramuscular therapy had been commenced the red cell count was 4,100,000.

In a patient known to respond only slowly to large amounts of stomach or liver extracts given by mouth, no response occurred following administration of a yeast extract given parenterally, an alcohol extract of yeast, bakers' yeast or liver extract given by mouth, but a slow rise occurred when whole liver was taken. E. G. (No. 1396) had been treated a year before, when the erythrocyte count was 2,650,000. The administration of 40 gm. of ventriculin daily at that time was associated with a reticulocyte rise of 3.2% (expected percentage 9) and the erythrocyte count rose only when double this amount was given.

On this admission, when the erythrocyte count was 2,180,000, a yeast extract (Y₂), prepared somewhat differently from that given to patients L. D. and J. M., was given intramuscularly, 3 cc. daily for 2 doses and then 6 cc. daily for 8 doses. This, as well as a 65% alcohol extract of yeast in doses corresponding to an amount of yeast representing 2 gm. per kg. body weight daily for 4 days and 5 gm. per kg. for 3 days, caused no reticulocytosis and the red cell count gradually fell. The injection of liver extract (J. H. H.) in 5 doses of 1.5 cc. and 5 doses of 3 cc. was followed by an increase of reticulocytes to 15.2% on the 8th day (expected percentage 23) and a rise in the erythrocyte count.

The patient returned 4 months later, again somewhat anemic but with no complaints. He had taken no treatment for almost 2 months and then took bakers' yeast somewhat irregularly. (R.B.C., 2,890,000; M.C.V., 108 c.μ.) He was given bakers' yeast (F), 1.5 gm. per kg. per day for 10 days. On the 6th day reticulocytes were 4.4% but the red cell count failed to increase. A similar quantity of brewers' yeast (M) was then given for 10 days. No reticulocyte increase occurred and the blood was unchanged. The dose of brewers' yeast was doubled (3 gm. per kg.), but even this large amount failed to produce a hematopoietic response. Liver extract (Lilly, 343) was then given, 16 gm. daily for 8 days, 24 gm. daily

* I am indebted to Dr. W. K. Waller, University Hospital, for his assistance in this case.

for 9 days. The last dose is the amount derived from 600 gm. liver. Even this large quantity of liver extract was without significant effect. Only when whole liver, $\frac{1}{2}$ pound daily, was consumed did the erythrocyte count begin to rise.

Comment. Maintenance Treatment. A number of patients whose blood was already normal, or nearly so, were given yeast in place of the oral or parenteral liver therapy they had been taking. These patients have been studied in the out-patient department and have been allowed to take their usual diets, without liver. Ten have received this treatment for 4 to 10 months (Table 2), while several others have been given yeast for shorter periods of time. Two of the 10 (E. R. and M. K.) were also given yeast while in relapse and their histories are recorded above.

TABLE 2.—CASES ON MAINTENANCE TREATMENT WITH YEAST.

Patient.	Age.	Sex.	Weight, kg.	Average dose of yeast, gm. per kg.	Duration of treat- ment, months.	Volume of packed red cells, cc. per 100 cc. blood.	
						At start.	At present.
L. E. . .	65	F	68	0.7	10	39.0	39.3
N. H. . .	39	F	70	0.3	9	40.0	42.0
E. R. . .	69	F	75	0.3	10	40.3	39.8
G. S. . .	48	F	59	0.5	8	40.2	40.0
M. A. . .	63	F	55	0.3	7	40.8	40.0
E. W. . .	65	F	64	0.7	6	40.0	43.4
J. S. . .	54	M	73	0.8	6	47.0	42.0
C. M. . .	61	F	56	0.4	4	37.0	39.2
M. K. . .	45	M	77	0.5 "N"	2	42.2	43.8
				0.3 "F"	2	43.8	31.8
J. G. . .	61	M	82	0.8	4	44.0	44.0

The quantity of yeast consumed has ranged from 0.3 to 0.8 gm. per kg. body weight daily. The yeast used was a brewers' type (N or M), except in several cases for a period of 2 months when a bakers' yeast (F) was given. These patients were subsequently given brewers' yeast again.

In all but 1 of the cases, the blood has remained essentially unchanged (Table 2). The single instance of relapse occurred in a patient (M. K.) who had chronic bronchitis and was subsequently shown to respond poorly to oral therapy (see above, Fig. 5). When he was first seen the erythrocyte count was 3,710,000, the volume of packed red cells 42.2 cc. He took brewers' yeast (N), 0.5 gm. per kg. per day, for 2 months. There was symptomatic improvement and the red cell count increased to 4,400,000, the volume of packed red corpuscles to 43.8 cc. For the next 2 months he took bakers' yeast (F) in smaller doses (0.3 gm. per kg.). The erythrocyte count dropped to 3,000,000, the volume of packed red cells to 31.8 cc.

Effect on Symptoms. In the patients treated with yeast while in relapse, when a hematopoietic response was obtained, symptomatic improvement like that associated with liver therapy occurred as

well. It was often difficult to induce the patients in relapse to take large amounts of yeast but after a few days, sometimes even before the reticulocytes had commenced to increase, appetite improved and even 120 to 150 gm. of yeast were readily consumed daily. Some patients have expressed preference for yeast as compared with liver, while others complained of distention or even nausea. In a few cases, nausea, vomiting and diarrhea developed, even when small quantities of yeast were being taken. It is impossible to say whether these symptoms were always due to the yeast, because some of these patients had been able to take yeast without trouble before, and in some instances they have taken it since these symptoms developed. One patient (E. R.) who complained of distention took liver for a few days instead and, finding the distention even more severe, resumed yeast which she has taken ever since.

Sore tongue developed in 2 cases (G. S. and B. A.) while yeast was being taken. In G. S. (Table 2), with continuation of treatment, the pain disappeared although the tongue remained beefy red. Sore tongue has always been this patient's chief complaint and this symptom had previously recurred while she was receiving oral liver therapy. It had been effectively relieved only by parenteral liver therapy. Parenteral liver therapy was also necessary for the relief of patient B. A.'s glossitis. The main complaint of patient C. M. (Table 2) was sore tongue. Temporary relief followed yeast therapy. When glossitis recurred, liver extract (Lilly, 343), 8 gm. daily, was given. After several weeks some symptomatic improvement occurred, even though the blood remained the same throughout the periods of yeast and liver therapy. None of the remaining patients were troubled by glossitis.

The patients described in this report had minimal neurologic symptoms and signs. In such cases it is difficult to evaluate the effect of therapy on the nervous system until treatment has been continued for a long time. Consequently comment here on this aspect of the treatment of pernicious anemia by means of yeast is omitted.

Discussion. As has been observed frequently in connection with the response of different individuals to liver or liver extracts, especially when orally administered,¹⁹ there was considerable variation in the response of these patients to yeast. In 3 cases (C. B., E. R. and G. Y.) brewers' yeast in amounts of 1.5 to 2.2 gm. per kg. body weight daily, produced reticulocyte responses which were greater than the average expected values³ following the daily use of liver extract derived from 600 gm. fresh liver, and a rapid increase in the erythrocyte count followed. In 1 case (L. D.) brewers' yeast, in doses of 1 gm. per kg. daily caused a well-marked reticulocytosis even after a good reticulocyte response to suboptimal amounts of desiccated hogs' stomach had occurred, and very rapid regeneration

of red cells followed. The same yeast caused a satisfactory hemopoietic response in patient C. V. The submaximal reticulocytoses in these last 2 cases were obviously due to the fact that a substantial reticulocytosis to other substances had already occurred.

Submaximal responses occurred in patients B. A. and L. E. S. to brewers' yeast given in quantities of 1 and 1.5 gm. per kg., respectively. In 1 of these (B. A.) subsequent parenteral liver therapy failed to produce further response than was obtained from yeast, and in the other (L. E. S.) the response to liver was submaximal. In 3 cases (M. K., M. T. and E. G.) brewers' yeast caused slight or no reticulocytosis and no significant increase in the red cell count, but liver extract in amounts derived from 300 to 600 gm. of liver, given by mouth, also failed to produce an increase in the red cell count although in 2 of these patients (M. K. and M. T.) reticulocytosis of equal degree to that following oral yeast therapy occurred. In 1 of these patients (M. T.) even parenteral liver therapy did not produce an optimal effect. Only in 1 patient (L. B.) was liver extract given orally followed by a definitely better response than that which followed administration of brewers' yeast given in doses of 1 or more gm. per kg. In another patient (M. Th.), whose response to oral therapy was poor, desiccated hogs' stomach was somewhat more effective than brewers' yeast.

As already mentioned, 9 patients receiving brewers' yeast as maintenance therapy have remained well to date, 4 to 10 months after commencement of this form of treatment.

Bakers' yeast (F) was given to 6 patients. In none did a satisfactory response occur. In 2 patients (L. B. and L. E. S.), brewers' yeast given subsequently in the same amounts caused a definite hematopoietic effect although in neither case was this as marked as has been observed in other cases. In 4 patients (S. B., J. M., J. Mc. and E. G.) the absence of a significant response to bakers' yeast was followed by a similar failure of oral liver therapy, and parenteral treatment with liver was necessary. In addition to these cases, relapse occurred in 1 patient (M. K.) while he was taking bakers' yeast as maintenance therapy.

It should be emphasized that the patients who were the subjects of the experiments reported here presented the clinical picture which is generally accepted as that of classical pernicious anemia. The opinion has been expressed that macrocytic anemia due to deficiency of extrinsic factor, rather than of intrinsic factor as occurs in pernicious anemia, may be readily confused with the latter, and Groen and Snapper¹⁴ recently described several such cases. Unlike Groen's cases, however, our patients not only had achlorhydria but there was the total lack of gastric secretion and low combined acidity characteristic of pernicious anemia, as well as persistence of achylia after the anemia had been relieved; many of our patients had suffered

one or more relapses following discontinuation of liver therapy, whereas Groen's patients remained well for a long time on a mixed diet not deliberately supplemented with liver; and finally, with one exception, there was no history of defective diet. This last argument is not stressed, however, because it is difficult to obtain accurate accounts of a patient's diet.

In view of the length of the periods of observation and the number of cases studied, the hematopoietic effects associated with the administration of yeast do not appear to be fortuitous. It seems fair to say that dehydrated brewers' yeast when given orally, may cause a hematopoietic response in cases of pernicious anemia which is as great as that produced by oral administration of liver extract derived from a quantity of liver 2 to 8 times the weight of the brewers' yeast used. Even when it is recalled that dehydrated brewers' yeast contains only 9% moisture, while that of fresh liver is much greater, the antianemic effectiveness of dehydrated brewers' yeast compares favorably with that of liver.

In his well-known experiments,⁶ Castle showed that when the gastric juice of normal persons is mixed with beef muscle, the "intrinsic factor" normally secreted by the stomach interacts with a dietary or "extrinsic" factor to form an "antianemic principle" which is effective in causing a hematopoietic response in cases of pernicious anemia in relapse.

In view of the fact that yeast has been regarded as a good source of extrinsic factor, it is important to know whether the action of yeast in these cases was due to the fact that enough intrinsic factor was secreted by the stomachs of these patients to convert the yeast into antianemic principle. This question is all the more important since it has been demonstrated¹¹ that the intrinsic factor deficiency in cases of pernicious anemia may not be absolute. Two groups of experiments were carried out in an attempt to answer this question.

Five patients were fed beef muscle, 200 gm. daily for periods of 7 to 15 days. In 4 no change whatever occurred in the blood. Three of these (S. B., M. K. and J. M.) responded poorly to the subsequent oral administration of yeast or liver extract, but 1 (G. Y.) responded promptly and rapidly to brewers' yeast after the blood had not changed under a 14-day régime of beef muscle. The fifth patient (C. V.) is also of great interest because the administration of meat was followed by a reticulocytosis which, though not great, was quite definite and was followed by some increase in the erythrocyte count. This patient, as has already been mentioned, was the only one from whom a history of inadequate diet had been obtained. The reticulocytosis produced by the beef muscle was followed by a second reticulocyte response when brewers' yeast was administered and a more rapid regeneration of red cells, indicating the greater potency of the yeast as compared with the beef muscle.

It should be pointed out that in the comparisons between the

antianemic effectiveness of beef muscle and yeast, the differences in the quantities of protein given were relatively small, and could not account for the differences in the effects produced. On the basis of its nitrogen content, 200 gm. of beef muscle, according to our determinations, contains 39.7 gm. of protein. The quantity of "protein" ($N \times 6.25$) administered in yeast to patients first given this amount of beef muscle ranged from 38.9 to 70 gm. daily. In the case in which the most striking difference between the effectiveness of beef muscle and yeast was noted (G. Y.), the quantity of protein given as beef muscle was 39.7 gm., that given as yeast was 43.5 gm. Furthermore, it should be noted that the quantity of protein in bakers' and in brewers' yeast is the same. Yet a well-marked difference in hematopoietic effect between these two types of yeast has been observed.

In 2 patients yeast was given, at first alone and then after mixture with normal gastric juice. According to Castle's hypothesis, if yeast acts as a source of extrinsic factor, no effect should follow its administration alone but a hematopoietic response should occur when it is given together with normal gastric juice. In the first patient (E. R.), a large quantity of brewers' yeast was given daily for 10 days. A well-marked reticulocyte response occurred. When a similar quantity of yeast was given together with gastric juice from normal persons, no secondary response appeared, indicating that the first effect had been maximal. In the second patient (B. A.), a smaller quantity of yeast was given. A moderate increase in reticulocytes followed. When the same quantity of yeast was given together with gastric juice, a secondary response was observed. This is exactly similar to the effect of mixing gastric juice from normal persons with liver or liver extract.²⁰

While these experiments do not exclude the possibility that yeast contains extrinsic factor in so high a concentration that even a minute amount of intrinsic factor can convert it into effective anti-anemic substance, it seems at least equally plausible that the anti-anemic factor in yeast differs from that in beef muscle not only quantitatively, but also qualitatively. Yeast has been shown in these studies to resemble in antianemic effect the factor or factors in liver and in desiccated hogs' stomach which are effective when given by mouth.

It has not been proved that the yeast factor is the same as the liver substance which is effective when given parenterally. In 2 patients (L. D. and J. M.) reticulocytosis followed the injection of yeast extract; but, since no well-marked increase in the number of red corpuscles followed, this effect may have been non-specific.

At this time one is not justified in drawing conclusions regarding the nature of the antianemic substance in yeast. It should be pointed out that our understanding of the physiologic disturbance in pernicious anemia is as yet very inadequate and that, although

reference is often made to "extrinsic factor," "intrinsic factor" and "antianemic principle," as if their chemical nature and mode of interaction has already been made quite clear, our knowledge of them is very imperfect. Only recently, Castle and his coworkers⁷ have brought evidence that an "intermediate substance" is formed by the interaction of the dietary and gastric factors.

Studies are now being carried out which seek to define some of the properties of the yeast factor. Neither the aqueous nor the alcohol extracts which have been prepared so far, have demonstrated a high degree of potency, although it should be noted that both of the patients to whom the alcohol extract was given (J. M. and E. G.) were shown later to be unsatisfactory for oral tests, and the choice of cases for testing the aqueous extracts (L. B., M. T. and M. K.) was not much better. Of greater interest are the comparisons of the antianemic effectiveness of brewers' and bakers' yeast. Although the data do not prove that antianemic substance is totally lacking in bakers' yeast, they demonstrate that "brewers'" yeast is at least more potent in this respect than "bakers'" yeast. This statement applies, of course, only to the dehydrated yeasts used in these studies but the observation is of considerable interest in view of the fact that there are differences in the manner in which the brewers' and bakers' yeasts used were grown. There is no reason to believe from our present data that the species of yeast is important.

There is no positive evidence at the present time that the yeast factor is one of the recognized water-soluble vitamins. Much of the work undertaken in the studies of yeast recorded in the literature was carried out with the object of discovering what relationship exists between the antianemic principle, or Castle's extrinsic factor, and the "B" vitamins. For this purpose studies have also been made of sources of these vitamins other than yeast, such as wheat embryo,²⁴ egg-white, rice polishings,¹⁸ riboflavin,² and nicotinic acid.¹⁵ None of these has been successful in demonstrating a relationship between one of the "B" vitamins and antianemic substance.

In conclusion, it should be emphasized that these observations are recorded because of the bearing they may have on an understanding of the disease pernicious anemia, rather than with the purpose of proposing a new form of treatment. Although some patients may prefer yeast to liver, the development of liver extracts for parenteral as well as oral use is such that, in general, this method of treatment will probably be desired. Knowledge of the distribution of anti-anemic substances and their precursors is of importance, however. Moreover, in view of Castle's hypothesis, it is of interest to know whether "antianemic principle" can be produced by a plant without the interaction of substances of animal origin. Furthermore, it may be that a study of yeast may lead to information regarding the antianemic principle and its precursors which it has not been

possible to gain so far by a study of liver. It is along these lines that present investigations are being directed.

Summary. 1. The results of the administration of dehydrated brewers' and bakers' yeast, as well as extracts of these substances, to 15 cases of pernicious anemia in relapse and 8 additional cases with little anemia, are described.

2. Maximal hematopoietic responses occurred in 5 patients given dehydrated brewers' yeast in amounts of 1 to 2 gm. per kg. body weight daily.

3. Submaximal effects occurred in 2 other patients who subsequently were found to respond inadequately to liver. Little response was noted in 3 patients who likewise failed to respond to oral liver therapy. Only in 1 case was liver extract, given by mouth, more effective than brewers' yeast, and in 1 resistant case desiccated hogs' stomach was somewhat more effective than brewers' yeast.

4. Nine patients receiving 0.3 to 0.8 gm. yeast per kg. daily as maintenance therapy, have remained well to date, 4 to 10 months following commencement of this form of treatment.

5. Brewers' yeast induced hematopoiesis without preliminary mixture with gastric juice from normal persons. The effects of the administration of yeast together with normal gastric secretion in 2 cases were similar to those observed when liver or liver extract is given in this way.

6. Four patients given 200 gm. beef muscle daily failed to respond to such treatment; while in 1, in whom a hematopoietic effect did occur, a secondary response to yeast appeared.

7. The difference between the antianemic effect of beef muscle and of brewers' yeast cannot be explained on the basis of differences in the quantity of protein administered.

8. A bakers' type of yeast failed to cause well-marked hematopoietic effects in 6 patients, 4 of whom subsequently did not respond even to oral liver therapy but 2 of whom responded to brewers' yeast.

9. Reticulocytosis occurred in 2 patients given yeast extracts parenterally but a significant increase in the number of red corpuscles did not follow.

10. A significant hematopoietic effect has not been produced by the oral administration of extracts of yeast which have been prepared so far.

11. No conclusion is reached regarding the nature of the hematopoietic substance in yeast, but the differences between the effects of brewers' yeast and "extrinsic factor" as represented by beef muscle, and the similarity of these effects to those produced by liver or liver extracts given orally, are pointed out.

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VITAMIN C DEFICIENCY—CLINICAL AND THERAPEUTIC PROBLEMS.

WITH A CASE STUDY OF SIX PATIENTS IN ONE FAMILY.

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SCURVY and allied conditions have been covered exhaustively in the literature of the past 5 years, over 1000 articles dealing with vitamin C having appeared in 1935 alone. It seems appalling, therefore, that this disease should be as prevalent as it is today. The fact that it is actually being precipitated by prescribed courses of therapy indicates that many physicians are failing to recognize the problem because of a belief that scurvy was a scourge in the past, but today is to be associated only with extreme poverty and malnutrition. On the contrary, it is very commonly found, even among the better economic groups, if the physician is acute to the possibility.

It appears worthwhile to review briefly the mechanisms by which hypovitaminosis C may be produced, the common signs and symptoms, the disease syndromes under which it may masquerade, and the criteria for diagnosis, before presenting the report of a mother and 5 adult children exhibiting varying forms and degrees of vitamin C deficiency as a result of familial distaste for its principal food sources. Although well able to afford a balanced diet, they almost never took citrus fruits, tomato juice, or cabbage. The most severe case, that of the mother, has been followed for 21 months, determinations of urinary vitamin C having been made daily for 4 months and weekly thereafter, as well as regular observations of the clinical course of the scorbutic condition by means of the capillary fragility test.²¹

Mechanisms by Which Hypovitaminosis C May be Produced. A. Increased demand for vitamin C, as in infections.^{1,11} B. Destruction of vitamin C, suggested by inability of some individuals to utilize oral doses. C. Deficient absorption due to altered chemistry of the gastro-intestinal tract or bacteria.^{14,17} D. Increased excretion of vitamin C, as is said to occur with indiscriminate use of salicylates.² E. Idiosyncrasy and, or, hypersensitivity for citrus fruits and other foods rich in vitamin C. F. Restriction of vitamin C-containing foods (Sippy diet, colitis diet, faddist diet, poor economic condition.)²¹

Common Signs and Symptoms of Scurvy.^{8,18} A. Bluish, swollen, spongy gums which bleed easily, or loose teeth. (Gums are usually healthy if teeth have been removed. Dental caries are considered by some workers to be caused in certain instances by vitamin C deficiency.) B. Dry scaly skin. C. Perifollicular hemorrhages. Hemorrhages under the toe nails. D. Tendency to hemorrhage (either petechial or ecchymoses into skin and, or, subcutaneous tissue). E. Brawny, tender swellings or indurations in calves, thighs, abdominal wall, popliteal space, and over the tibia. F. Weakness, pain in limbs and joints especially after exercise. G. Palpitation and breathlessness. H. Anemia not amenable to liver or iron therapy. Microcytic, macrocytic, or normocytic in type. Responds to vitamin C with reticulocytosis and recovery. I. Constipation or diarrhea with offensive and bloody evacuations. J. Hematuria. K. Night blindness, while usually associated with vitamin A deficiency, may also be a symptom of vitamin C deficiency. L. Loss of weight. Anorexia. M. Slight edema. N. Fever.

Disease Syndromes Under Which Scurvy May Masquerade. A. Rheumatism and allied diseases. B. Erythema nodosum. C. Lupus erythematosus. D. Varicose veins with varicose eczema. E. Hemorrhagic nephritis. F. Purpura hemorrhagica, thrombocytopenia and other purpuras. G. Hemophilia. H. Gingivitis. I. Neuritis. J. Colitis or gastro-intestinal malignancy, especially when hemorrhage is a prominent feature. K. Unexplained secon-

dary anemias. *L.* Other peripheral vascular diseases. *M.* Optic hemorrhage. *N.* Osteomyelitis.

Diagnostic Criteria. *A.* Increased capillary fragility^{4,8,9,21} when the following diseases and conditions have been ruled out: lues, tuberculosis, kidney diseases, acute infectious diseases, the blood dyscrasias, menstruation, arsphenamine poisoning and gastric achylia. *B.* Under vitamin C therapy alone a return of the fragility to normal with clinical improvement.^{*21} *C.* A history of deficient vitamin C intake, or the consumption of large amounts of salicylates.² *D.* One or more signs or symptoms listed earlier.¹⁸ *E.* When judiciously evaluated, the chemical tests for cevitamic acid content of body fluids,^{5,7} including the saturation determination by the test dose method.²² As previously pointed out, these tests indicate only the state of saturation of the tissues but not *per se* the disease scurvy.

Case Reports. **CASE 1.**—The mother, aged 64, in good financial circumstances, was first seen August 21, 1936. The chief complaint was pain in calves after walking one-half block, 8 months' duration. Past history: 8 months previously, the patient developed intermittent claudication in calves after walking half a block necessitating resting for 2 or 3 minutes before walking could be resumed. About 8 weeks before the first visit, she developed pain in both tibiae, which medication did not relieve; the pain was present whether at rest or exercising. Two weeks before the first visit, discrete red, raised spots appeared along the inner side of left leg, followed in 1 or 2 days by pitting edema of both legs. The reddened areas increased rapidly in size and coalesced. She stated that she thought her "legs would burst."

She has had symptomless hypertension of 10 years' duration (200+ systolic pressure). Seven years ago, she developed a syndrome diagnosed as arthritis, which was preceded by a condition in her legs similar to the present one; however, at that time, several of the reddened raised areas ruptured, requiring many months to heal, with deep scar formation. She states her legs have never been normal since that time. She recalls a return of her so-called arthritis each spring with tibial pain and edema of legs with the symptoms less severe during the summer. The present attack has persisted since early spring and is by far the most severe.

Systems all negative. Seven pregnancies, 5 living children. Family history—negative.

Physical Examination. Well developed, well nourished, white female, obviously in great pain. Eyes: negative; grounds showed sclerosis of vessels. Nose and ears: negative. Mouth: mucous membranes and gums normal; upper and lower dental plates. Chest: heart enlarged to left, rate 88, rhythm regular, loud systolic aortic murmur; blood pressure 184/78; lungs, clear throughout. Abdomen: negative. Extremities: Heberden's nodes of terminal phalanges; oscillometric readings from popliteal arteries distally were zero bilaterally; extending from the internal malleolus to just below the knee, the skin and subcutaneous tissues were hard and indurated; a fluctuating mass was palpable over the left tibia. There were many raised irregularly-shaped tender red areas over the rest of the leg. The right leg was entirely free of these spots. However, both legs showed many perifollicular hemorrhages. A marked decrease in temperature of both legs from

* Method used in these studies was that described by Wright and Lilienfeld.²¹ Normal—up to 10 petechial spots; borderline zone, 10 to 20; pathologic, above 20.

the middle of the legs down to the toes was noted, more pronounced in the left. Both legs had 2+ edema.

Capillary Fragility. One hundred petechial hemorrhages in 5 minutes (the arm became so hemorrhagic that the test was terminated at one-third the usual time. Technique used was that described by Wright and Lilienfeld).²¹

Laboratory Results. Urine, negative; 2-hour renal function test (Mosen-thal), normal. Wassermann, negative.

Blood chemistry:

Non-protein N	45 mg. %	Chlorides	460 mg. %
Urea N	14 mg. %	CO ₂ C.P.	52.8 cc. %
Uric acid	3.2 mg. %	Serum proteins (total)	5.4%
Sugar	85 mg. %	Albumin	3.6%
Cholesterol	150 mg. %	Globulin	1.8%

Diagnosis. 1. Scurvy. 2. Essential hypertension, enlarged heart. 3. Occlusive vascular disease of vessels of legs from popliteal artery distally. Arteriosclerosis. 4. Chronic rheumatoid arthritis.

Present Illness. For 7 years this patient had been under treatment for rheumatoid arthritis and had at intervals taken large amounts of salicylates. At the same time, she was on restricted vitamin C intake because of an idiosyncrasy for citrus fruits and the ordinary vitamin C-containing foods. Coincidentally, her protein intake had been greatly curtailed because of her hypertension.

When the patient was first seen, August 21, 1936, she had been suffering from what had been diagnosed as arthritis since early Spring, and her condition was becoming progressively worse, even though she was taking salicylates in ever-increasing amounts. At this time her legs were in far worse condition than they had been with previous attacks. The malady had been diagnosed on one occasion as erythema nodosum, on another as lupus erythematosus; biopsies had been performed to diagnose the condition without success. The present attack was diagnosed as a rare peripheral vascular disease.

In view of this patient's history and physical findings, together with the fact that sclerosis and scurvy are frequently associated,^{12,13} a diagnosis of scurvy was made and antiscorbutic treatment instituted. When the scurvy was under control, the vascular angle was treated in the conventional manner.³

The initial intravenous dose of crystalline cevitic acid* was 100 mg., dissolved in 5 milliliters of water, and subsequent doses of 1000 mg. were given twice a week for the first month. In addition to the intravenous therapy, 300 mg. were given orally (six 50-mg. tablets), and citrus fruits to the extent of 16 to 24 ounces were included in her daily diet. Within a month marked clinical improvement was noted and the capillary fragility had reached zero.

When we felt that the danger of a relapse had passed, the intravenous therapy was reduced to once a week and the daily oral administration depended upon to keep the patient saturated. This dosage of over 300 mg. of cevitic acid a day seemed almost unnecessarily large, since Schultz,¹⁵ Wright²⁰ and others demonstrated cures of scurvy on administration of from 40 to 60 mg. a day. However, on November 21, 1936, when she had been under treatment for 3 months, she complained of severe pretibial pain, which she stated had been present for 5 days. Examination revealed a new subperiosteal hemorrhage over the tibia of the left leg. A capillary fragility test done at this time produced 50 petechial hemorrhages in 15 minutes. The intravenous cevitic acid therapy was increased to twice

* The crystalline cevitic acid used in these studies was supplied through the courtesy of Merck & Co., Inc., Rahway, New Jersey.

a week, together with the daily oral administration and supplementary fruit juices, which under ordinary circumstances should have been sufficient to saturate the patient and prevent further relapse. Unfortunately, this dosage was apparently insufficient to do what was expected, for on December 4, 1936, she had a relapse more serious than the preceding one.

About noon, she developed motor and sensory aphasia and weakness of the legs. At 6 P.M., she was incoherent, unable to stand, and had twitching of the face. At 9 P.M., she recognized people but was still aphasic. She had urinary and bowel retention. Her condition was diagnosed as due to either cerebral hemorrhage, in which case scurvy was the precipitating factor, or cerebral thrombosis. In 24 hours, her right-sided paralysis was pronounced and a cord bladder added to the difficulties. In 10 days a left basal pneumonia and cystitis supervened.

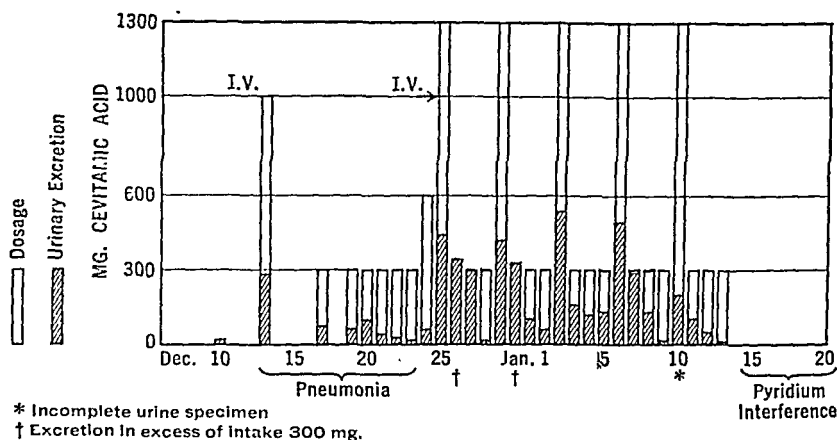


CHART 1.—Relation of urinary excretion of cevitamic acid to intake, in Case 1. (Dosage oral unless marked I. V. (intravenous). The 1300 mg. taken on 5 separate days was composed of 1000 mg. intravenously and 300 mg. orally.)

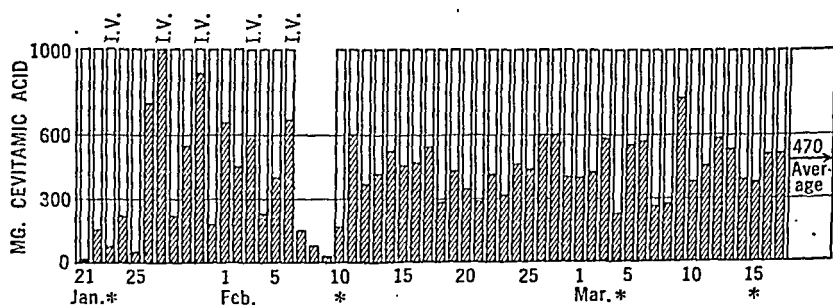


CHART 2.—Continuation of Chart 1. (For 10 months following March 17, in determinations made weekly, the average level of excretion was 470 mg. per 24 hours.)

At about this time we started determinations of the urinary vitamin C (for record covering 15 months, see Charts 1 and 2). Twenty-four-hour specimens were collected under standardized conditions,²⁰ namely, in amber glass bottles containing sulphuric acid and preserved at icebox temperature. They were titrated at pH 3 using a modification of Harris and Ray's⁷ procedure with dichlorophenol indophenol. Pyridium used in treatment of the cystitis was found to give erroneously high vitamin C

results. A detailed description of this mode of interference has been described elsewhere.⁶

During the febrile period of pneumonia, the urinary vitamin C excretion dropped to a low point, as in the experience of Bullova.¹ The course of the pneumonia was uneventful and is of no significance here. It required 4 months for full recovery of function of the extremities, and 5 months for complete disappearance of the motor and sensory aphasia.

Until February 6, 1937, intravenous cevitic acid was administered 2 or 3 times a week until thrombosis of the veins of her arms made it impossible to continue this mode of therapy. The intramuscular route¹⁰ could not be used because of the size of the dosage required and objections of the patient. Twenty-four ounces of citrus fruit juices were given on each of the next 3 days to determine if she could get enough vitamin C this way, but on the third day the excretion had dropped to 27 mg. To insure a wide margin of safety, 1000 mg. of crystalline cevitic acid in $\frac{1}{4}$ glass of water were given orally each day, as well as at least 6 ounces of fruit juice (tomato, pineapple, grapefruit or orange) and with this medication alone the patient remained symptom-free for 10 months during which time the urinary excretion averaged 470 mg. a day.

Early in November, 1937, illness in the family caused her a great deal of concern and worry, and on December 4 (1 year after the cerebral accident) she suffered another relapse, manifested by pains in the tibiae, edema of the legs, dry scaly skin, and an indurated area in the right calf. The capillary fragility test showed 45 petechial hemorrhages in $7\frac{1}{2}$ minutes, and saturation test performed the same day gave a result of 530 mg. (of 1000 mg. intravenously) excreted in the first 5 hours. The marked fragility did not support the interpretation of normal vitamin C nutrition that the chemical test would indicate. Injections of 1000 mg. were given intravenously 3 times a week, the same dosage orally the other days, and in 2 weeks the fragility was down to 22 per $7\frac{1}{2}$ minutes. At the time of writing (May, 1938) the capillary fragility is still slightly above normal, 22 per 15 minutes, although normal vitamin C saturation results are being obtained. During the last 5 months the crystalline cevitic acid has been given orally each day, 2000 mg. one day and 1000 mg. the next, dissolved in a small quantity of water and added to the juice of 1 orange; this has been in an effort to introduce the synthetic vitamin into the stomach in a natural medium, in which there are thought to be agents that delay oxidation of this vitamin and which may also contain some factors that enhance its antiscorbutic properties. (For tabulation of above data, see Table 1.)

Comment. The problems encountered in the handling of this case have been numerous but they have shown the need for further study of precipitating factors in scurvy, of the proper evaluation of the present laboratory methods, and especially investigation of the utilizable form and fate of cevitic acid in the human economy.

Scurvy was presumably precipitated in this individual by insufficient intake of foods rich in vitamin C, decreased absorption resulting from the generalized vascular changes of advancing age, and possibly increased excretion of the small supply in other foods by salicylate medication. Gastric achylia¹⁶ was not present in this patient.

As the body is not able to store large amounts of vitamin C, a patient's daily requirement must be determined. Van Eekelen's¹⁹

investigations have indicated that the average human requirement for adults is about 60 mg. a day. This individual, however, needed more than 300 mg., which was the original dose, because almost none of this was excreted (see December 23 and 28, 1935, and January 9 and 13, 1936, in Graph 1). When 600 mg. were given (on December 24), the urine content was 50 mg. As the symptoms of scurvy reappeared on the 300 mg. dosage, and the 600 mg. permitted a little excretion, the requirement would appear to be close to 600 mg. This is also suggested by the fact that the urinary excretion on the 1000 mg. oral dose leveled off at 470 mg.

TABLE 1.—TABULATION OF DOSAGE OF VITAMIN C, THE CAPILLARY FRAGILITY COUNT, AND CLINICAL NOTES OF CASE 1.

Date.	Previous intake of vitamin C.	Capillary fragility count.	Clinical notes.
(1936) 8-21	Rarely took citrus fruits	100 in 5 min.	First visit, tibial pain, edema of legs, numerous hemorrhagic areas on one leg.
8-26	300 mg. crystalline orally daily. 24 oz. citrus fruit juices	Edema less. No pain.
8-29	100 mg. intravenously initial dose. Orally as above each day	72 in 7½ min.	No edema. Subperiosteal hemorrhage still present. No pain.
9-5	1000 mg. intravenously, b.i.w. Orally as above	45 in 15 min.	As above. Hemorrhagic areas slowly decreasing in size.
9-12	As above	34 in 15 min.	As above.
9-19	As above	29 in 15 min.	As above.
9-26	As above	0 in 15 min.	As above.
11-21	1000 mg. intravenously once weekly. Orally as above	50 in 15 min.	Tibial pain past 4 days. New large subperiosteal hemorrhage.
11-25	1000 mg. intravenously b.i.w. Orally as above	Able to sleep through night without pain. Walks 3 to 4 blocks without pain. Remarkably improved.
12-4	As above	Relapse, cerebral accident.
12-13	1000 mg. intravenously 3 times a week	Pneumonia.
(1937) 2-10	As above	Symptom-free. Thrombosis of veins prevented further intravenous medication.
12-4	1000 mg. orally daily for past 10 months	45 in 7½ min.	Relapse, tibial pain, edema, dry skin, indurated area in calf of leg.*
12-11	1000 mg. intravenously 3 times a week. Orally on other days	35 in 7½ min.	Symptom-free.
12-18	As above	22 in 7½ min.	Symptom-free.
(1938) 1-20	As above	18 in 7½ min.	Symptom-free.
5-10	1000 mg. and 2000 mg. orally on alternate days	22 in 15 min.	Symptom-free.

* Vitamin C saturation test—530 mg. excreted in 5 hours.

Why she suffered a return of symptoms and an increased capillary fragility after a 10 months' regimen which included 1000 mg. orally every day, is difficult to understand. The 24-hour urinary output continued to be about 500 mg., and an intravenous test dose always returned over 500 mg. in 5 hours. This apparent saturation with the anti-scorbutic vitamin is difficultly understood because intravenous administration every other day for 2 weeks was accompanied by a lowering of the fragility count. The question arises whether this last relapse may have been due to altered metabolism

caused by anxiety, or the possibility that synthetic crystalline cevitamic acid may have some fractions which cannot be utilized by this individual, thereby increasing further the dosage needed to maintain her in adequate nutritional balance, or that a deficiency had occurred of some anti-hemorrhagic factor other than vitamin C. Studies along these lines are being continued.

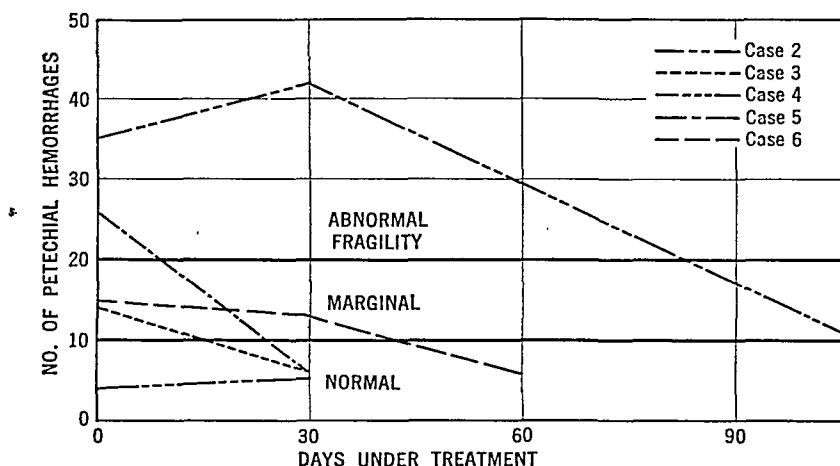


CHART 3.—The effect of cevitamic acid administered orally, 1000 mg. each day on the capillary fragility of the 5 children of Case 1.

Studies of the Patient's Children. After this patient had been under treatment for 5 months, studies were made of her 5 adult children, all of whom complained of lack of strength and frequent upper respiratory infection. They had rarely eaten citrus fruits because of a familial distaste for them. Since diagnosis of their mother's vitamin C deficiency, however, fruit juices had been taken about twice a week. Vitamin C saturation tests performed at this time showed that all were subnormal or low-normal; and with the capillary fragility test, 2 exhibited marked fragility, 2 marginal, and 1 normal. A course of treatment with large doses of crystalline cevitamic acid was followed by normal responses in every case (see Chart 3) and disappearance of symptoms.

It should be noted that these studies were made, not when the subjects were at their usual level of negligible vitamin C intake, but after they had begun to add some citrus fruits to their diet. Since the studies performed at this stage showed undersaturation of the tissues and increased capillary fragility, both of which conditions responded to vitamin C therapy, we feel inclined to attribute the symptoms of these persons to hypovitaminosis C. Presentation of their individual cases follows:

CASE 2.—Daughter, aged 21, college student, chronically fatigued, frequent attacks of upper respiratory infection, severe dysmenorrhea, joint

pains, history of rheumatic fever, mitral disease. Urine examination was normal, Roentgen ray of chest was negative, and Roentgen ray of sinuses showed moderate membranous infiltration left ethmoid, slight involvement of both antra with thickening of floor of right side.

She had an attack of rheumatic fever 13 years ago. For the next 10 years she had been incapacitated for at least 2 weeks of each year by severe pains in the ankles and knees; for all these attacks, salicylates had been administered. Three years ago tonsillectomy and extraction of 5 teeth was followed by alleviation of symptoms except for occasional mild joint pains. She had eaten almost no citrus fruit in her life. Upon examination she mentioned that she felt so tired after school that she had to take an hour's rest. She also suffered from a severe sinusitis. Blood studies revealed the red blood cells to be 4,030,000; hemoglobin (Sahli), 92%; white blood cells, 7300; stab neutrophils, 16%; segmented, 30%; large lymphocytes, 4%; small lymphocytes, 36%; monocytes, 6%; and eosinophiles, 8%. The red cells showed definite macrocytosis. The capillary fragility test produced 35 petechial hemorrhages in 15 minutes, and the vitamin C saturation result was 470 mg. (of 1000 mg. intravenously) excreted in 5 hours. The recent intake of vitamin C-containing foods had apparently saturated the tissues to a moderate extent, but had not yet effected complete repair of the perforated capillary walls.

Following oral administration of 1000 mg. of crystalline cevitamic acid daily for 1 month, the fragility test showed 42 petechial hemorrhages. After continuing this dosage for 3 months, the count fell to 11. During these same 3 months, liver was administered parenterally twice a week. At the end of this time, the blood count showed red cells to be 4,480,000; hemoglobin, 87%; white cells, 6300; stab neutrophils, 8%; segmented, 38%; monocytes, 10%, and no eosinophiles. The change from eosinophilia before treatment to the present eosinopenia as well as the increase in monocytes and lymphocytes would seem to indicate immuno-healing effort. In the red cells, the anisocytes had decreased 45%. The patient now felt so much stronger that she required no more than the night's rest.

During the summer months the crystalline form of the vitamin was discontinued, but citrus fruits were taken daily; the liver therapy was discontinued. She spent the greater part of each day in the sun on the beach. In the latter part of August, however, medical advice was sought for a pansinusitis and a recurrence of weakness. Her blood count had decreased to red blood cells, 4,080,000, and hemoglobin, 77%. With restoration of crystalline vitamin C (1000 mg. every third day) the sinus condition has been held in check and physical strength maintained.

This is another case somewhat similar to that of the mother, that links rheumatism and rheumatic fever to hypovitaminosis C. Rhinehart and his associates have reported findings suggesting that scurvy predisposes to rheumatic fever. In this individual, it is impossible to say whether there was any causative relationship between the two, but in the light of Daniels and Everson's report of increased excretion of vitamin C following administration of acetylsalicylic acid, it is interesting that the one child who had suffered from rheumatic fever and recurrent rheumatism in which salicylates was the choice of therapy, should have the highest capillary fragility, and that it should fall to normal on administration of optimum doses of vitamin C.

CASE 3.—Daughter, aged 26, complained of extreme fatigue, nervousness, poor circulation in the extremities, loss of appetite, sinusitis. Urine and chemical blood examinations were normal, physical examination and Roentgen ray of chest, negative.

Because of marked distaste for citrus fruits, this patient had not taken any "since she could remember." One year before, during a cold, she had tried to eat an orange but suffered an upset stomach, possibly as a psychological or allergic reaction. When her mother's vitamin C deficiency was diagnosed, she managed to drink the juice of 3 oranges a day for 3 days when urticaria developed on the face. When the fruit was withdrawn, this disturbance disappeared. Later all citrus fruits were slowly added to her diet with no reaction.

When examined here, the blood count showed a hemoglobin (Sahli) of 72%, and red blood cells, 4,080,000. The capillary fragility test produced 14 petechial hemorrhages in 15 minutes, and in a study of vitamin C saturation, 390 mg. were excreted in 5 hours. After taking crystalline cevitic acid, 1000 mg. daily for 1 month, the capillary fragility count fell to 6.

For the last 2 years she had been under medical care for secondary anemia. Virtually all this time liver and iron pills had been taken, but the hemoglobin stayed between 67 and 72%, and the red cell count between 3,500,000 and 3,800,000. A course of ultraviolet treatments was ineffective. When liver was administered parenterally twice a week for 12 weeks, the hemoglobin remained the same but the red cell count rose to 4,300,000. After 300 mg. crystalline cevitic acid (six 50-mg. tablets) had been taken together with tablets of a liver and iron preparation daily for 6 weeks, the hemoglobin rose to 82% and the red cell count to 4,620,000. At this time the patient felt vigor unknown for some years. Plenty of fruit juices were taken with the liver and iron. In less than 2 months, however, a return of weakness was explained by a hemoglobin of 76 and red cell count of 4,190,000. Restoration of crystalline cevitic acid was accompanied by a return of strength as well as improvement of the red count within a month to 4,420,000.

This case seems to represent the type of anemia, described by Mettier and Minot¹² which is responsive, not to liver and iron therapy alone, but to adequate vitamin C nutrition.

CASE 4.—Daughter, aged 29, fatigued, frequent upper respiratory infections, recurrent painful ulcers on the mucous membranes of the cheeks, gums and tongue.

This is the only member of the family whose capillary fragility was within the normal range, namely, 4 petechial hemorrhages in 15 minutes. Her vitamin C saturation result of 400 mg. (of 1000 mg.) excreted in 5 hours, however, was borderline. A blood count showed the hemoglobin (Sahli) to be 78%, the red blood cells, 3,840,000, and the white blood cells, 6100. The red cells showed macrocytosis and microcytosis. Because of the questionable state of vitamin C nutrition indicated by the small response to the test dose, crystalline vitamin C was prescribed as well as parenteral liver injections. The liver was given biweekly for 12 weeks and the cevitic acid, 1000 mg. orally each day for 1 month and biweekly thereafter. At the end of this course, the hemoglobin had risen to 95, the red cells to 4,250,000 and the white cells to 9200. Anisocytosis of the red cells had decreased 50%.

The liver and crystalline cevitic acid were discontinued and citrus fruits depended upon to maintain adequate vitamin C nutrition. After 6 months during which the ulcers appeared less frequently, they finally

ceased to recur. In the past year she has maintained a high standard of health, avoiding colds for the first time in several years.

It is difficult to say whether this recovery was brought about by the liver or the vitamin C, but considering her history of very low vitamin C intake, and the fact that she has remained symptom-free since the liver therapy was discontinued, on a diet containing adequate vitamin C, there seems to be a definite possibility that her case was partly due to hypovitaminosis C.

CASE 5.—Daughter, aged 32, complained of fatigue, irritability, and frequent upper respiratory infection.

This patient had received two courses of iron injections during the past 5 years for a persistent anemia in which the hemoglobin fluctuated between 60 and 70%. Each winter had brought on such decrease in strength that she had had to leave her work for a week or more and go to a warmer climate. When examined here, her blood count revealed a red cell count of 3,760,000, a hemoglobin (Sahli) of 88%, and moderate macrocytosis. In a test of vitamin C saturation, 460 mg. (of 1000 mg. intravenously) were excreted in 5 hours. Although, according to this result, her tissues would seem to have achieved a slight degree of saturation by the recent addition of vitamin C-containing foods to her diet, the capillary fragility count was 26 petechial hemorrhages in 15 minutes. Oral administration of 1000 mg. of crystalline cevitic acid each day for 1 month resulted in a decrease of the fragility count to 6.

After liver had been given parenterally twice a week for 3 months, accompanied by large doses of the crystalline vitamin (1000 mg. biweekly, orally) the red cell count was 4,390,000, with a decrease in the number of anisocytes. In the year since then, nothing has been prescribed except adequate fruit juices, and yet vigorous health has been maintained. She has had no colds for the first winter in several years.

This more thorough recovery than that of other years may have been brought about by the improved vitamin C nutrition. In view of her history of very low citrus fruit intake and her marked capillary fragility that became normal after a course of cevitic acid therapy, it would appear probable that the heretofore chronic anemia may have been largely due to deficiency of vitamin C. Studies of Minot and Mettler^{12,13} have shown that some anemia is caused, not so much by lack of the metallic elements, iron and copper, as by subminimal vitamin C nutrition.

CASE 6.—Son, aged 34, excessive fatigue, bleeding gums, chronic sinusitis. The blood count of this patient seemed normal, showing a hemoglobin (Sahli) of 92% and a red cell count of 4,740,000, but he complained of feeling extremely tired by mid-afternoon and of requiring a great deal of sleep. His gums bled very often, and he had a chronic sinusitis. On examination, the capillary fragility count was 15 petechial hemorrhages in 15 minutes, and the vitamin C saturation result was 375 mg. (of 1000 mg. intravenously) excreted in 5 hours.

Since the capillary fragility was borderline and the saturation result subnormal, even though he had lately added citrus fruits to his diet, crystalline cevitic acid (1000 mg. orally each day) was prescribed. After 1 month the fragility count was 13, and after another month it had fallen

to 6. The bleeding of the gums ceased, and has not recurred in the past year during which fruit juices have been taken daily. The sinusitis has subsided to a great extent and there is no longer the feeling of excessive fatigue.

The combination of symptoms and clinical observations suggestive of vitamin C deficiency, all of which became normal on administration of the crystalline form of the vitamin, point to the likelihood that his vague illness was caused by hypovitaminosis C.

As in the cases of the other children, the recent intake of vitamin C-containing foods was no doubt responsible for the finding of a borderline rather than a marked deficiency of the vitamin.

Summary. The causes, symptoms and criteria for the diagnosis of scurvy are reviewed. The case reports of a mother and 5 children in good financial circumstances present varying degrees of hypovitaminosis C, resulting from distaste for and consequent restriction of foods rich in this vitamin.

Determinations of cevitic acid content of the body fluids by the present laboratory methods require careful evaluation, and cannot take the place of thorough clinical study.

Since the principal patient described required about 500 mg. of crystalline cevitic acid intravenously daily to bring about chemical saturation and disappearance of symptoms, and later relapsed while receiving 1000 mg. orally each day, the question arises whether this is due to a metabolic peculiarity of this individual which changes the vitamin into a non-antiscorbutic form, or whether the potency of the synthetic substance may be altered by mechanical handling, storage conditions, or as yet unrecognized factors in the methods of administration, or thirdly, whether a deficiency of some factor other than synthetic vitamin C produced her scorbutic-like syndrome.

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DETERMINATION OF THE CODEHYDROGENASES I AND II (COZYMASE) IN THE BLOOD OF DIABETICS IN SEVERE ACIDOSIS.*

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OBSERVATIONS on a large series of pellagrins during the past 8 years have shown that not infrequently clinical pellagra develops in patients with diabetes mellitus, and that pellagrins in acute relapse rapidly become worse when restricted to diets of large amounts of glucose. Pellagrins in relapse excrete in the urine increased amounts of an ether-soluble substance, or substances, giving the color of porphyrin in 25% HCl. This substance disappears promptly from the urine following the administration of nicotinic acid and reappears when nicotinic acid therapy is discontinued.⁶ We used the same method to test the urine from a patient in diabetic coma but with no clinical evidence of pellagra and the results were similar to those observed in pellagrins.⁵ Recent observations by Vilter, Vilter and Spies,^{8a,b} showing that the blood from patients with chronic leukemia and from pellagrins in relapse contains less cozymase and coferment than normal blood and that the content of these coenzymes in the blood of pellagrins can be raised by oral administration of nicotinic acid, led us to apply the same method in the study of the blood [from 3 cases of diabetes mellitus. The present report is concerned with this study.

Method. Five cultures of *B. influenzae* and *B. parainfluenzae* were carried on chocolate agar slants, and studied in broth sub-cultures. The broth was prepared with 2% Difco proteose-peptone, 0.6% salt and 2% human blood. This medium, pH 7.6 was heated to 95° C. and filtered; a portion was sterilized by filtration through a Seitz filter and another portion was autoclaved. As was expected, the portion of autoclaved medium was found not to support growth of those members of the influenza group studied, since cozymase, factor V, is destroyed by autoclaving. The unautoclaved medium, in contrast, provided luxuriant growth of these organisms, as has been shown previously by Davis¹ and by Thjötta and Avery.⁷

The procedure was as follows: 1 cc. of venous blood was added to 19 cc. of sterile distilled water and heated in a water-bath at 85° C. until the color of the solution became brown. The solution was cooled, and after the

* This investigation was aided by grants to the University of Cincinnati College of Medicine from the John and Mary R. Markle Foundation, the Busch Fund, and the David May Fund.

addition of 1 to 2 drops of sterile N/10 HCl was centrifuged. The supernatant fluid was then added to tubes of autoclaved peptone broth so that the final dilutions of blood added to the prepared medium represented volumes ratios of 1/1000, 1/2000, 1/4000, 1/8000 and 1/12,000. The blood was heated at 85° C. so the proteins could be centrifuged out, and so the labile inhibitory substance in the serum, described by Rivers and Leuschner³ would be partially or totally destroyed.*

This method has been found to be extremely sensitive. In controlled experiments, the addition of a solution of cozymase to autoclaved broth produced heavy growth at a concentration of 1 part per 100 million. Moreover, the sterility of the media and of all the reagents was proved by control tubes set up with each experiment.

Selection of Cases. Three patients admitted to the Cincinnati General Hospital in severe diabetic acidosis (blood carbon dioxide combining power less than 20 vol. %) were selected for study. Case 1 (J. B.), a white boy, 14 years of age, without previous knowledge of diabetes, had been eating large quantities of an adequate and varied diet until he became drowsy the day of entry. Case 2 (E. M.), a negress, had been vomiting for 8 days before admission. Case 3 (E. W.), a negress, had taken no insulin and eaten little food for a week before entry since she had been incapacitated by an acute upper respiratory infection. In none of the cases was there clinical evidence of pellagra nor of severe systemic disease other than diabetes mellitus. Each patient made a satisfactory recovery following routine therapy, consisting of parenteral administration of large quantities of insulin, physiologic saline and a 10% glucose solution. In each case the blood of a member of the hospital staff served as a control for the diabetic blood under investigation.

Observations. As shown in Table 1, the admission blood of the cases suffering from severe diabetic acidosis, when inoculated with loop transfers from a 12-hour culture of *B. influenza*, supported growth of this organism in dilutions of 1/2000 or less. In contrast, the blood of the control series invariably supported growth in dilutions of 1/8000 or more.

Following excellent responses to the routine diabetic therapy described above, determinations of growth factor present in the blood were repeated within an interval of 10 days. The blood of Case 1 was found to support growth of the influenza bacillus in dilutions up to and including 1/8000. Similarly, the blood of Case 3, after the much shorter interval of 3 days, supported growth well in the 1/4000 dilutions.

Case 2 was maintained for 3 days following return of consciousness on a diet of orange juice and egg white. During the last 48 hours of this period, she was given orally 500 mg. of nicotinic acid, and then her blood was retested for growth factor. Although her blood at the outset, supported minimal influenza growth in the 1/1000 dilution only, following nicotinic acid therapy, *B. influenza* grew

* Dr. H. I. Kohn (Biochem. J., 32, 2075, 1938) has published recently a method similar to ours.

well in the 1/8000 blood dilution. Likewise, increased amounts of prophyrin or substances resembling porphyrin were found in her urine before nicotinic acid therapy and disappeared after the drug had been administered.

TABLE 1.—TWENTY-FOUR-HOUR GROWTH OF *B. INFLUENZÆ* IN DILUTIONS OF BLOOD IN AUTOCLAVED PEPTONE-BLOOD BROTH.

Diabetic patients in coma.		Dilutions of blood.					R.B.C.	Nicotinic acid given, mg.	Porphyrin-like substance in urine.
		1/1000.	1/2000.	1/4000.	1/8000.	1/12,000.			
Case 1 (J. B.)	12/12/38	+	#	—	—	—	5.9	..	Not done.
Case 2 (E. M.)	12/23/38	#	—	—	—	—	5.5	..	Positive.
Case 3 (E. W.)	12/31/38	++	#	—	—	—	Negative.
+18 nicotinic amide in each tube		++	—	—					
+18 nicotinic amide and 1 cozymase in each tube		+++	+++	+++	+++				
+1 cozymase in each tube		+++	+++	+++	+++				
Same diabetic patients after routine treatment and subsequent recovery.									
Case 1 (J. B.)	12/22/38	++++	+++	++	#	—	4.8	..	Not done.
Case 2 (E. M.)	12/26/38	+++	++	+	+	—	4.74	500	Negative.
Case 3 (E. W.)	1/ 3/39	+++	++	++	—	—	4.7	..	Negative.
Normal cases used as control to viability of culture for each of above cases.									
J. F.	12/12/38	++++	+++	++	+	#			
W. F.	12/23/38	++++	+++	++	#	#			
S. P. V.	12/31/38	++++	+++	++	#	—			
W. F.	12/22/38	++++	+++	++	#	#			
S. P. V.	12/26/38	++++	+++	++	#	#			
R. W. V.	1/ 3/39	++++	+++	++	+	—			

NOTE.—The extent of growth was interpreted as follows: ++++ = very heavy; +++ = heavy; ++ = moderately dense; + = light; # = just perceptible; — = no growth. The controls of the culture in autoclaved medium without added blood were negative in each case. The sterility of the blood which was added was also established.

Lwoff and Lwoff² have shown that bacilli of the influenza group require a codehydrogenase for growth, and are unable to synthesize it from its components, nicotinic acid amide, adenylic acid, ribose and phosphoric acid. In a previous paper^{2a} it has been shown that such a factor is decreased in the blood of pellagrins in relapse and is restored by administration of nicotinic acid. Whether a similar

restoration could be aided by administering the other components of the enzyme through a mass action like effect is plausible but as yet untried. The evidence advanced above indicates that a similar factor is deficient in the blood of diabetics in severe acidosis. That this factor is cozymase is supported by the following evidence.

A sample of cozymase* was dissolved in distilled water, so that 1 cc. contained 10 γ . Three series of autoclaved tubed media containing 1/1000, 1/2000 and 1/4000 dilutions of admission blood from Case 3 were prepared. Eighteen γ nicotinic acid amide were added to each tube of the first series, the same amount of nicotinic acid amide and 1 γ cozymase to each tube in the second series, and 1 γ cozymase alone to each tube of the third series. The results were conclusive. Those tubes containing cozymase supported luxuriant growth in all dilutions, while those containing nicotinic acid amide alone were equivalent to the untreated diabetic blood, for growth took place only in the 1/1000 dilution. Control tubes showed that the cozymase solution was sterile after filtration and that it alone in concentrations of 1 part in 100,000,000 would support growth in the autoclaved media.

Conclusions. 1. This report shows that the blood of patients suffering from severe diabetic acidosis supports the growth of *B. influenzae* to much less extent than does the blood of normal individuals or the same diabetic when regulated or given doses of nicotinic acid.

2. The codehydrogenase I (cozymase) when added to such deficient blood or to autoclaved media without blood supports luxuriant growth of the influenza bacillus, although nicotinic acid amide shows no such growth stimulation.

3. These observations show that not only is codehydrogenase I deficient in the blood of pellagrins in relapse, but also in the blood of diabetics in severe acidosis, and support the hypothesis that the therapeutic effect of nicotinic acid depends upon the synthesis in the body of nicotinic acid nucleotide and finally of a codehydrogenase.

(Note added to the proof by the author). Spies and Koch⁴ have shown that brewers' yeast (Anheuser-Busch, Inc., The Harris Laboratories, Mead Johnson & Co.) and liver extract (Lilly No. 343) both contain cozymase as evidenced by their ability to support growth of *B. influenzae* under the conditions of the method described in this study. Corn meal, which is one of the major constituents of the pellagra-producing diet, also supports growth to some extent, but not nearly so well as does the yeast or liver extract which are anti-pellagric materials. Spies and Koch have shown that 20 normal persons, carefully chosen because they were in good health and were known to eat adequate amounts of a well-balanced diet, excreted cozymase in the urine. In these 20 cases dilutions of 1 to 100, and often dilutions of 1 to 1000, supported growth of the *B. influenzae*. Repeated examinations of the urine of a patient (C. K.) with chronic lymphatic leukemia showed that it supported growth of the *B. influenzae* in dilutions of only 1 to 10, and her blood only in dilutions of 1 to 100. The administration of nicotinic acid, 500 mg. daily, by mouth, was followed by a transient increase in cozymase concentration in the blood and urine. Keeping the nicotinic acid intake constant, the addition of 100 gm. of dry brewers' yeast, by mouth, produced a definite increase to where the blood would grow *B. influenzae* in dilutions of 1 to 2000. After keeping the nicotinic acid and yeast therapy constant for several days, an injection of 20 mg. of riboflavin in sterile physiologic solution of sodium

* Obtained through the courtesy of Dr. Hans Molitor of Merck & Co.

chloride was given. This was followed by a spectacular increase in growth supporting activity through the 1 to 12,000 dilutions. Associated with this increase in cozymase content of the blood was a feeling of well-being, and the patient was able to get out of bed and aid in caring for other patients, despite the fact that her red cell count remained around 2,300,000. It is too early to know whether the blood cells are affected following elevation of cozymase in the blood, but persons having as low a concentration of cozymase as this patient might reasonably be expected to improve following a rise of cozymase content in the blood and tissues. On numerous occasions cozymase has been added to various inoculated tubes and invariably it has supported growth of these bacteria, indicating that the variation from the normal controls is the result of a deficiency of cozymase, or some substance which acts similarly, rather than some hypothetical inhibiting substance.

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THE RELATION OF POTASSIUM TO PERIODIC FAMILY PARALYSIS.

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In this paper we present data which were gathered on a patient with periodic family paralysis during the past 24 months in an effort to clarify the relationship of potassium (K) to the attacks of weakness in this disease. One of us⁴ has previously summarized elsewhere some of the results and discussed the problem in the light of recent literature. Older work had suggested that K citrate^{9,†} would sometimes shorten an attack, and Holtzapple⁶ had relieved seizures with KBr, although he attributed the result to the bromide rather than to the K. Japanese investigators^{10,12} had been able to induce seizures with adrenalin, sugar and insulin, all of which lower serum K. There was thus clear indication that K was in some way connected with the attacks. We found early that K salts in sufficient quantity would promptly cure the weakness, and that during

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† Supported by Kirby-McCarthy Fund.

‡ We wish to express thanks to Dr. W. S. McCann, Rochester, N. Y., for calling our attention to this reference; he examined a grandchild of this patient who still takes K citrate for the seizures.

attacks serum K was low. Aitken *et al.*¹ independently made the same observations and published their results prior to ours.

The immediate problem was to establish a more exact relationship between the lowered serum K and the muscular weakness and to seek the reason K fell in the attacks.

Clinical Abstract. The patient, a male, aged 16, suffered from the type of the disease in which attacks occur almost daily. The long period of observation served to establish the characteristics of the spontaneous seizures and enabled us better to judge the effects of various experimental and therapeutic procedures.

The attacks begin almost invariably in the early morning hours between 3 and 7 A.M. during sleep, and last into midmorning, or if severe, until evening. Recovery, once initiated, is prompt and complete. The body musculature suffers unequally; sometimes the arms are more affected, at other times the legs. Extensor muscles are usually weaker than the flexors. During the attacks the muscles are flaccid, reflexes are abolished, and the response to electrical stimulation is decreased or unobtainable. No sensory changes develop.

In spite of the severity of the disease the bulk and development of the muscles is excellent. The external genitalia are normal and sexual function is established, but the testicles are quite small. No other physical defects are present. Routine studies of blood and urine are normal.

The father is the only other member of the family with the disease; two younger siblings are healthy. The father was studied by Dr. Wm. G. Spiller and Dr. J. W. McConnell of Philadelphia in the earlier seizures; his attacks were less frequent and more prolonged than his son's, and have decreased in frequency as he has grown older. K salts will also relieve his weakness.

Methods. Serum and feces were analyzed for K by the chlorplatinate method of Hald,⁵ and urine by the same method with preliminary ashing with thorium nitrate after Strauss.¹¹ Samples were ashed and analyzed in triplicate; blanks and recoveries of added K were run daily. All data reported are based on samples ashed in silica containers; earlier analyses when ashing was performed in Pyrex were discarded because of irregularities in the measurements. The K estimations have a standard error of 2%.

Blood samples were taken without anticoagulant in centrifuge tubes and separated within 15 minutes. During the study of K excretion, a weighed diet calculated to contain not quite 3 gm. K per day was furnished in 3 different menus fed in recurring 3-day cycles.* Approximately equal quantities of distilled water were taken daily. Urine was collected at intervals selected for each experiment.

Relation of the Serum K Level to the Attack. During severe spontaneous seizures, the serum K level has fallen by as much as 30%. These observations agree with the findings of Aitken *et al.*¹ But in milder attacks the fall has been much less, at times only 5 to 10%, figures of the order of 4.79 m.eq. per L. being obtained during the seizure. In attacks induced by various means this relationship between severity of weakness and degree of lowering of serum K has not been so evident; thus after adrenalin the fall in serum K may be considerable even with a mild attack, while severe seizures set up by drinking large quantities of water may be accompanied by only a slight fall in K. In one experiment, November 20, 1937, the patient was well with a serum K of 5.44 m.eq. per L.; 2 hours

* We wish to express our thanks to Miss Marion Mowbray and Miss Eleanor Erickson, Dietitians in the Hospital.

later adrenalin (minims 10, 1 to 1000, hypodermically) was given which produced a mild attack within 20 minutes. In 45 minutes the patient could get out of a chair only with assistance; serum K had fallen to 3.73. When spontaneous complete recovery had occurred about an hour after the injection, the K had risen only to 4.15, a figure lower than has occurred in some mild spontaneous seizures. In a severe attack after a water diuresis, there was little fall in serum K (Fig. 1). The subject was normal with serum K of 5.44 m.eq. per L., showed slight weakness at 5.12, and was unable to move off the bed at a level of 5.00.

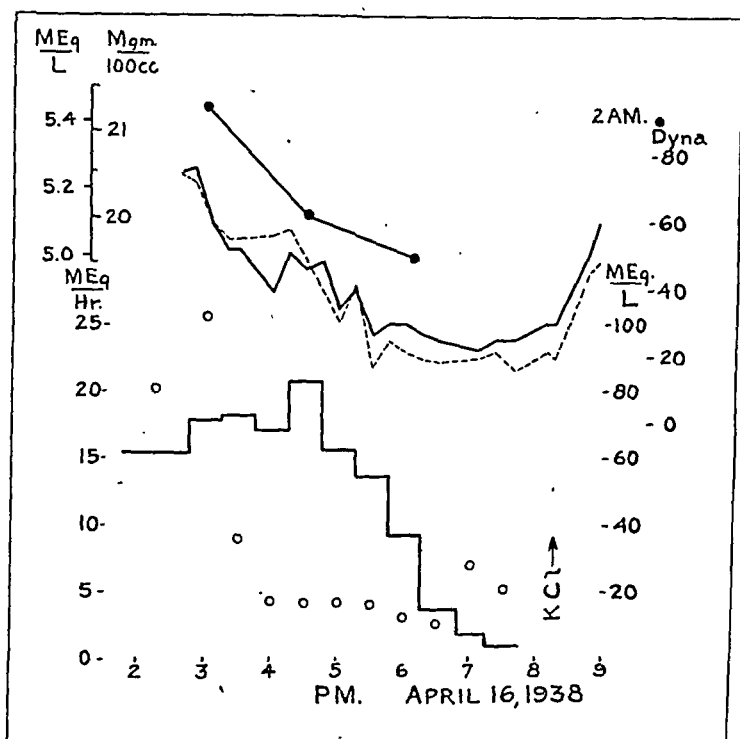


FIG. 1.—Effect of water diuresis following a large dose of K, in lowering serum K and inducing an attack. ●—● Serum K; against scale at left. ——— left hand; - - - - - right hand; dynamometer record of maximum grasp; read against scale on right. Columns at base show K excretion in urine; read against scale on left. ○ K concentration in urine; read against scale on right.

There is thus no constant level of serum K associated with transition from strength to weakness nor from weakness to strength; however, when the curve of K has been followed, the attack has developed with a falling, and the recovery ensued on a rising, serum K.

Potassium Excretion in Relation to Seizures. Reference has already been made to the fact that seizures could be induced by water diuresis; in each of three trials the attempt was successful. So far as we are aware this method of setting up an attack has not been observed before. It was thus of interest to determine whether the diuresis

led to the elimination of K in large quantities prior to the development of weakness. This was found to be the case, and accompanying the attack, as we have stated, serum K fell slightly.

In one trial, 6 glasses of water in 1 hour raised the potassium excretion rate from 9.9 m.eq. per hour to 16.5, five times the usual daytime excretion rate. When, after 2 hours, 29 m.eq. of K had been excreted in the urine, weakness began to develop.

The experiment performed April 16, 1938, is recorded in Figure 1. The patient had taken at noon 5 gm. KCl to relieve a severe attack; by 1 P.M. he was well. At 2.50 P.M. vigorous water intake was started; 350 cc. were consumed each half hour until 5.45 P.M., a total of 2.6 L. Weakness promptly developed as indicated by the dynamometer readings, and became so severe that by 6.15 he was just able to sit, and by 8.10 he could no longer rise to a sitting position. Thus a full attack developed despite the large dose of KCl at noon. The attack was terminated by another dose of KCl at 8.15; within 45 minutes his usual strength had returned. During the diuresis 73 m.eq. K (1.9 gm.) had been lost in $3\frac{1}{2}$ hours. Associated with this depletion of K, a severe weakness developed and the serum K fell from 5.44 m.eq. to 5.00.

As it was possible to induce attacks by means of a diuresis, we examined the urine prior to spontaneous seizures to see if a similar outpouring of K preceded the natural attacks. The patient was placed on the diet described above, and urinary and fecal K determined. The night urine was fractionated to obtain the periods preceding seizures. Fecal K was only followed long enough to determine that it varied little and was about 8 m.eq. per day. Urinary excretion was followed several weeks. A record of 5 consecutive days in Figure 2 is representative. The patient was in approximate balance, eliminating 53.5 m.eq. K per day. (The diet presumably contained 61 m.eq. daily.) A control subject on the same diet excreted 58.7 m.eq. per day (Fig. 3).

From the record it can be seen that K excretion at night was no higher preceding the day of an attack than preceding a normal day; nor was it greater before a severe seizure than a mild one. There is thus no evidence of a spontaneous K diuresis prior to the attack. During the seizure itself, K excretion falls. From these observations we may infer that the K which leaves the serum during the weakness is not eliminated, but probably enters other body fluids or tissues.

The daily rhythm of excretion of K shows there is a rapid elimination during the period of absorption from the gastro-intestinal tract, while at night excretion falls to low levels. The same rhythm is seen in the control (Fig. 3), but is exaggerated in the patient. The ratio of highest to lowest rate of excretion in the control was 5; in the patient, 15.

K Therapy. The attacks of weakness, as we have already stated, can be promptly terminated by K salts in sufficient quantity. In our patient, 2 to 5 gm. KCl by mouth were required, depending

on the severity of the attack. Other K salts were also effective but less useful because of undesirable side actions. Sodium salts, NaCl

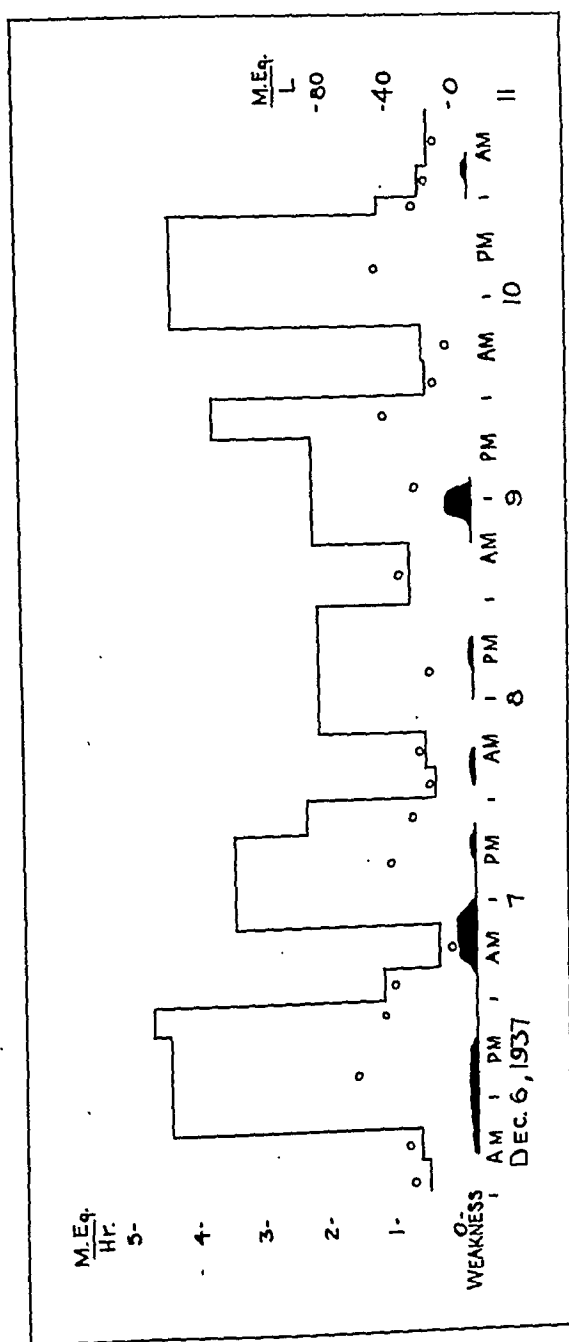


FIG. 2.—Patient R. E. ° K concentrations in urine; scale on left. Block columns: K excretion rate in urine; scale on right. Black patches at base indicate clinical weakness of legs and arms. Moderately severe attacks December 7 and 9. Adrenalin administered December 8 at noon, producing very slight attack.

and NaHCO_3 , were ineffectual as were creatin hydrate (15 gm. by mouth) and prostigmin (1.5 mg. hypodermically).

From the excretion studies it was clear that K given during the day would be rapidly eliminated and hence would not prevent noc-

turnal seizures. When we gave KCl at 2 A.M. (4 gm. together with a soup to prevent rapid absorption) we were able to keep the patient relatively free from attacks. Previous efforts to prevent night seizures by administration of K during the day had failed.

Discussion. It appears to us from the studies of this disease that the lowered serum K is not *per se* an adequate explanation of the weakness; for attacks have occurred with serum K within 10% of normal value and at a level which causes no weakness in normal subjects. Furthermore, McEachern⁷ has observed partial remission from an attack after small doses of K but without any associated elevation of the lowered serum K.

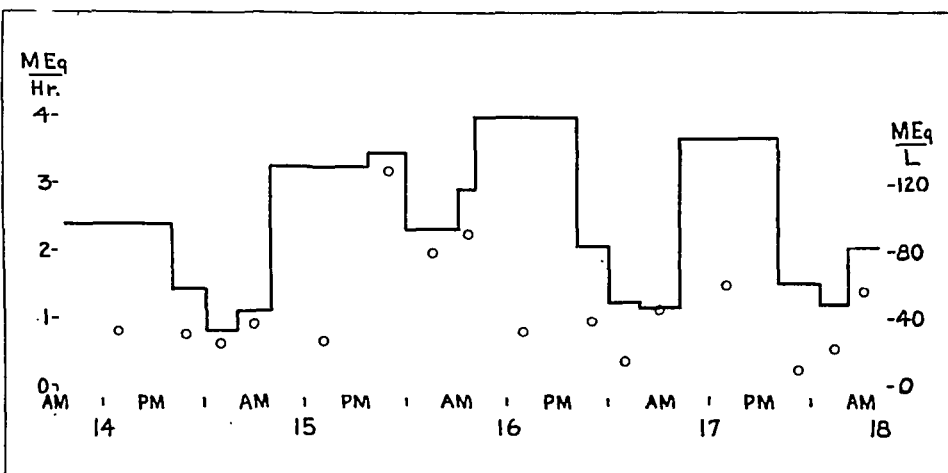


FIG. 3.—Control G. G. ○ K concentrations in urine; scale on right. Block columns: K excretion rate in urine; scale on left.

We next inquire whether the lowered serum K of the severer attack is preceded by excessive loss of K by excretion. In our experiment with water diuresis this is clearly the case. In the spontaneous seizures, however, our data give no evidence of exaggerated loss of K, either before or during the seizure.* Consequently, the fall of serum K in these attacks must result from transfer of K from serum to some other tissue or fluid, the site of which cannot be definitely assigned.

It may be that the K passes from serum to the disordered muscle in response to an abnormal demand for K, arising in the muscle as the attack comes on, and if so the fall in serum K is to be viewed as secondary or compensatory. By this hypothesis, as the attack develops, K is drawn from the available sources; when these fail, serum K falls. The more severe and more extensive the attack,

* Since this paper was written Allott and McArdle² have published a study in which they found no evidence of a K diuresis preceding the attack; and Ferrebee, Atchley and Loeb³ have read a paper before the Society for Clinical Investigation reporting in a similar case low serum K during attacks, no correlation with serum glucose or phosphate, marked drop in urinary potassium excretion during an attack, with following compensating increase in potassium excretion, increase of creatinuria during an attack, and alleviation and prevention of attacks from potassium chloride by mouth.

the greater would be the expected fall in serum K. When, as sometimes, the attack is confined to a few muscles, little or no fall in serum K might be expected. Attacks would be more frequent when the compensatory sources of K were depleted; consequently, attacks would tend to occur late in the night when no K was being absorbed from the gut or when, as after water diuresis, the reserve of K had been excreted. The tendency of adrenalin and glucose and insulin to bring on an attack may result from changes induced which are manifest in the transfer of serum K to the peripheral tissues.⁸ The relief of seizures by administration of K salts would be expected.

The various factors which are known to induce or relieve attacks can under this hypothesis be related. But as to the nature of the primary disturbance in the muscle, which creates the demand for K, there is at present no direct evidence.

Summary. In a patient with periodic family paralysis we observed a rapid loss through the urine of K absorbed from the gastrointestinal tract; in the late hours of the night the rate of K excretion was unusually low. Water diuresis rapidly washed K from the patient, with a fall in serum K and the development of a seizure.

Attacks of weakness were associated with a falling serum K and recovery with rising values. There was, however, no fixed level below which weakness developed. K salts were of use in preventing as well as curing seizures.

The attacks of weakness appeared to develop at times when the supply of K available for absorption or redistribution was depleted.

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SOME DIFFERENT TYPES OF ESSENTIAL HYPERTENSION: THEIR COURSE AND PROGNOSIS.

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SINCE the recognition of the clinical syndrome of essential hypertension 40 years ago, much has been learned in regard to its abnormal physiology and ultimate course. However, the question of etiology

still baffles investigators and, until its cause or causes are established, physicians should try to group their cases by the best available methods. Allbutt,¹ in 1896, believed that the outlook for some of these patients was good for many years. As the recognition of cases increased in number and as the use of the Riva-Rocci¹⁴ sphygmomanometer became general, many physicians, including Janeway,⁶ gradually realized that there were variations in the severity of the condition. This fact led Volhard and Fahr,¹⁶ in 1914, to speak of benign and malignant forms of the disease. Two of us began our joint study of our more serious cases in 1920 and, in 1928,⁹ reported the detailed findings in 81 cases of what was termed "the malignant hypertension syndrome." Many of the cases differed from the malignant hypertension of Volhard and Fahr and the malignant nephrosclerosis of Fahr,^{3a} in that a diagnosis frequently was made before there was serious impairment of retinal, cerebral, cardiac, and renal functions.

With further study, it became obvious that there were many cases of essential hypertension which did not belong in this group of rapidly progressive cases and could not be termed cases of benign or simple hyperpiesia. Gradually, a group could be identified in which the presence of mild vasospastic retinitis was an important diagnostic feature. The course was less rapid and remission of symptoms sometimes occurred. We have identified another group, the salient features of which are more marked hypertension and more distinct narrowing and sclerosis of the retinal arterioles than encountered in the benign cases, and yet there is no demonstrable break in retinal, cerebral, cardiac, or renal functions.^{7,8}

To avoid confusing descriptive terms, the groups have been given numbers. We have considered the usual benign cases as belonging to Group 1; those of more marked hypertension, presenting few untoward symptoms, without retinitis as belonging to Group 2; those of mild vasospastic retinitis as belonging to Group 3, and those revealing the so-called malignant hypertension syndrome as belonging to Group 4.

Kernohan,⁹ in examination of pathologic material obtained at necropsy in our cases of Group 4, found that changes in the arterioles were often widespread throughout the body. Similar findings since then have been reported by Scott, Seecof and Hill,¹⁵ Pilcher and Schwab,¹³ and Moritz and Oldt.¹² These facts suggested a study of the arterioles in tissue obtained by biopsy which would give information concerning the peripheral arterioles during life among cases of the four groups. Skeletal muscle was chosen because it represented a large portion of the weight of the body and was less subject to local disease which might involve the blood-vessels. The pectoralis major muscle was selected because of its accessibility.^{8,10} This study began in November, 1927, and, between that date and August, 1932, a period of 5 years, the arterioles of

muscle obtained from 138 patients who had hypertensive disease were examined. In addition to this histologic study of the arterioles of muscle in 138 cases belonging to the four groups, a follow-up record was kept of every case up to 1937, or approximately 9 years from the time when the first patient was examined and 5 years from the time when the last patient was examined. A follow-up study of the 81 cases belonging to Group 4, begun in 1920 and reported in 1928,⁹ has been continued so that now we have accurate data on the course of 146 cases of Group 4 and 219 cases belonging to all groups* (Table 1).

TABLE 1.—DATA AT TIME OF FIRST EXAMINATION.

Hypertension, group.	No. of patients.			Age, years.	
	Male.	Female.	Total.	Range.	Mean.
1	7	3	10	30-65	55
2	14	12	26	21-59	41
3	22	15	37	22-57	42
4	99	47	146*	8-64	40
Total	142	77	219		

* Biopsy of muscle was carried out in 65 cases.

Groups. *Diffuse Arteriolar Disease With Hypertension, † Group 1.* Many of the cases described by Allbutt,¹ Janeway,⁶ and others as cases of hyperpiesia or essential hypertension belong in this group. The hypertension can be of long duration without causing symptoms and without impairing general health. Cardiac and renal functions continue to be adequate and changes in the retinal vessels are minimal. Albuminuria may be of a slight degree or may be absent, and, in spite of the gradual development of hypertrophy of the heart, electrocardiologic examinations may give evidence of normal findings for many years. The hypertension as a rule does not rise to extreme heights, and among many individuals falls to normal levels during sleep. With moderate protection of the vascular system, the prognosis is usually good. Happily, the majority of cases encountered in practice fall into this group. As a rule, we found few anatomic changes in the arterioles of muscles so that biopsy was carried out in only 10 cases. The ages of these 10 patients, 7 men and 3 women, ranged from 30 to 65 years (mean, 55 years). Six patients are alive 7 to 9 years (86 to 105 months) after their first examination. Four patients are dead; 2 died of coronary disease, 1 of typhoid fever, and 1 of pneumonia.

Diffuse Arteriolar Disease With Hypertension, Group 2. Patients of this group have a higher and more sustained hypertension than those of Group 1. They may complain of being more nervous than

* These data were obtained by 1, subsequent visit and examination; 2, letter from patient or near relative; 3, letter from patient's home physician, and 4, statement from the State Bureau of Statistics in case of death, in certain instances.

† We prefer this term to that of essential hypertension because it stresses the importance of dynamic or organic changes in the arterioles. There are always, however, coexisting changes of varying degree in the arteries.

formerly, but their general health is good and their cardiac and renal functions are satisfactory. The changes in the retinal vessels are more marked than in Group 1, but retinitis is not present. Correspondingly, the arterioles of muscles are shown to have changes more frequently. In a study of these patients, the impression is obtained that the disease is more progressive than in cases belonging to Group 1. In our group of 26 cases, 14 men and 12 women, aged 21 to 59 years (mean, 41 years) data revealed that 9 patients were alive 6 to 9 years (74 to 107 months) later, and 17 were dead. It is of interest that one of the living patients was examined for the first time 10 years before biopsy was carried out in 1920 and, at that time, the systolic blood pressure was 210 mm. of mercury and the diastolic, 120. Thus, it appears that certain patients belonging to this group may live comfortably for many years.

Diffuse Arteriolar Disease With Hypertension, Group 3. In this group, the hypertension is often high and sustained. On palpation, diffuse changes in the arteries usually can be demonstrated such as thickened, rubber-like radial, brachial, superficial temporal, posterior tibial, and dorsalis pedis arteries. Although cardiac and renal functions may be adequate, sometimes there are minor alterations in function as indicated by dyspnea on exertion, characteristic changes in the electrocardiogram and nocturia. Nervousness, headache, and vertigo are often annoying symptoms and visual disturbances may occur. Albuminuria and microscopic hematuria may be present. An important criterion is the presence of angiospastic retinitis,¹⁸ together with definite sclerotic changes in the arterioles, but edema of the disks is not present. Changes in the arterioles of muscles are more numerous and more marked than among patients belonging to Group 1.

It is of great interest that, even in cases of Group 3, there may be a remission in the activity of the pathologic process. The patient feels better and stronger and headaches or vertigo may disappear. There is evidence in the retina of previously active retinitis and many small arterioles may become obliterated. In 1 such case, a number of small arterioles of the retina had undergone thrombosis and, on biopsy, the same process was seen to have taken place in some arterioles of the skeletal muscle. It is a question whether or not cessation of arteriolar spasm could be responsible for the remission.

In 37 cases of this group, 22 men and 15 women, the ages were 22 to 57 years (mean, 42 years). The prognosis was serious, because 79 to 90 months after examination, 34 patients were dead and only 3 were living. One of the latter is well, however, 7 years after biopsy of the muscle was made and the blood pressure has been as low as 130 mm. of mercury systolic and 90, diastolic.

Diffuse Arteriolar Disease With Hypertension, Group 4. All observers are agreed that patients belonging to this group are in a very serious condition. This fact is emphasized further by our

follow-up study which indicated that the great majority of the patients died within 1 year. The characteristic symptoms are nervousness, asthenia, loss of weight, headache, visual disturbances, dyspnea on exertion, and nocturia. Also, there may be obvious neurologic lesions. The objective findings are a persistently elevated blood pressure, palpable diffuse arterial thickening of the peripheral arteries, and retinal changes. The important retinal alteration is edema of the disks. There is also marked spastic and organic narrowing of the arterioles with diffuse retinitis. Albuminuria, cylindruria, and erythrocytes are usually present. Cardiac and renal functions may be adequate but, sooner or later, they become impaired. Associated with the terminal picture, there may be failure of the functions of the brain, heart, and kidney simultaneously. This fact suggests widespread anoxemia owing to decreasing arteriolar blood supply. The arterioles of muscle of 65 patients were examined by biopsy. As was to be expected, the abnormal findings were more frequent and more marked than in any of the other groups but, in a few cases, they were slight or absent. The ages in this series of 146 cases, 99 males and 47 females, were 8 to 64 years (mean, 40 years). The prognosis was very serious; 79% of the patients were dead within a year. However, among a few patients, the course is not so rapid. Some patients even have periods of subsidence of the retinitis accompanied by clinical symptoms which suggest remission. One of our patients is alive, 11 years after her first visit. Similar cases belonging to Group 3 were considered previously. Thus, in Group 4 also, spasm of the arterioles¹⁸ may determine whether the condition is progressive. Such subsidence of severe retinitis was noted by Liebreich¹¹ who gave the first detailed description of the ophthalmoscopic findings in cases of albuminuric retinitis in 1859. Fishberg and Oppenheimer,⁴ in 1930, reported in a case of malignant hypertension the healing of severe retinitis with no recurrence over a period of $4\frac{1}{2}$ years. We reported a similar case in 1929 and, since that date, have seen 4 additional cases. We have observed a few cases of Group 4 in which the course was very rapid. The significant symptoms were sudden severe headaches, gross hematuria, and pains in muscles, accompanied by a persistently high blood pressure, marked narrowing of the retinal arterioles without apparent sclerosis and absence of distinct changes in the arterioles of muscles. A progressive, angiospastic mechanism seems to offer the best explanation.¹⁸ Evidence is also accumulating that, even when there is marked pathologic change in the arterioles, as in some cases of Group 4, compensatory mechanisms, at present obscure, still may permit periods of improved metabolism in tissues and a reasonably comfortable existence.

To distinguish clinically between the four groups usually is not difficult. Some patients may have to be observed over several

months to determine whether they belong to Group 1 or 2. A given case may be markedly progressive so that although at first examination it appears to belong to Group 1 or 2, it may rapidly assume the characteristics of Group 4. On the other hand, there are cases in which there is little progression over a period of many years; a majority of these belong to Group 1, but a moderate number to Group 2 and a few to Group 3. Because the arterioles throughout the organs of the body seem to be the chief point of attack and can be visualized readily only in the retina, the findings obtained on ophthalmoscopic examination are very important. Patients who have only mild narrowing (increased tonus) or sclerosis of the retinal arterioles usually will fall into Group 1. Patients usually are placed in Group 2 if they have moderate to marked sclerosis of the retinal arterioles, whether of the chronic type, characterized especially by exaggeration of the arterial reflex and arteriovenous compression, or of the postangiospastic type characterized especially by generalized and localized irregular narrowing of the arterioles. Thrombosis of retinal veins or retinitis of the arteriosclerotic type may occur among patients of this group.

Patients who have retinitis of the angiospastic type, characterized especially by edema, cotton-wool patches, and hemorrhages in the retina superimposed on a combination of sclerotic and spastic lesions in the arterioles, belong to Group 3. If measurable edema of the disks is added to this picture the case belongs to Group 4. Diffuse retinitis and edema of the disks may develop in association with active spastic narrowing of the arterioles in certain cases of hypertensive disease of acute onset.¹⁷ This type of retinitis may subside at times without the development of additional anatomic changes in the arterioles which characterize the typical case of Group 4.

Histologic Study of Arterioles of Muscles. The histopathologic study of the arterioles in small portions of the pectoralis major muscle obtained by biopsy in this series of cases has confirmed the previous work of Kernohan, Anderson, and Keith⁸⁻¹⁰ that organic changes in such vessels do occur in cases of hypertensive disease. As previously noted and confirmed by Moritz and Oldt,¹² the most consistent change was an increase in the thickness of the arteriolar wall. The ratio of the diameter of the lumen to the thickness of the wall was found to be decreased. Following the plan of Kernohan, Anderson, and Keith,¹⁰ in each biopsy at least four representative arterioles cut in cross-section were measured, four measurements being taken of the wall and two of the lumen. The mean of these measurements then was computed and a ratio was obtained by dividing the mean diameter of the lumen by the mean thickness of the wall. The mean of the ratios of the four or more representative arterioles obtained by measuring each specimen, gives a figure which has been used for each case. The mean ratio in the normal arteriole is 2.0 (1.7-3.0).

In addition to quantitative changes in the walls of the arterioles, we have observed certain other changes from the normal which we have termed qualitative. These include an increase in the number and size of the nuclei in the arteriolar muscle in association with and more or less commensurate with the decrease of the ratio. Also, we have observed an increase in the number and size of the nuclei in the intima of the arteriole, organized thrombosis, and evidence of arteritis and periarteritis as indicated by the presence of lymphocytes and fibroblasts in the media and adventitia. Also, in some cases, usually those whose ratios of lumen-to-wall were reduced definitely, arterioles have been found in which the lumen was completely closed without the presence of thrombosis. In no instances have we observed necrosis or degenerative changes in the arterioles, such as have been described as existing in vessels of the kidney of comparable size. It has been suggested that the reduced ratio of lumen-to-wall might be entirely the result of arteriolar spasm which was so persistent that it did not relax even after removal of the tissue from the body. The work of Moritz and Oldt has shown that this change can be reproduced neither by variations in histologic technique nor by vasoconstricting drugs in animals. The qualitative changes seen in the arterioles are further evidence that the changes are organic and that diffuse organic arteriolar injury may take place in cases of hypertension.

A careful analysis of the data obtained from the examination of the arterioles of muscles of 138 of the cases represented in this paper has shown that the changes are not consistent and that there is not a definite correlation between the findings in the arterioles of muscles and the division of cases into the four groups, the clinical severity of the disease, the length of life of the patient after the biopsy was taken, or the changes in the retinal arterioles. For example, there are some patients of Group 4 who died within a few months and had marked changes in the retinal arterioles but who had very few changes in the arterioles of muscles. Also, there are some patients in Groups 1 and 2 who are still living after more than 5 years and who had minimal changes in the retinal arterioles but who exhibited rather marked reduction of the ratio of lumen to wall and, also, definite qualitative changes in the arterioles of their muscles. However, when all the data are analyzed, it is found that, in general, a greater percentage of patients who have marked changes in the arterioles of muscles belong to Group 4 (Tables 2 and 3), have corresponding changes in the retinal arterioles and have a more serious prognosis. Thus, of 9 patients who had sclerosis of the retinal arterioles, Grade 0 to slight, only 25% had a ratio of lumen-to-wall of the arterioles of muscles of less than 1.4, although, in 81 cases of sclerosis of the retinal arterioles, Grade 1 to 2, 70% had a ratio of less than 1.4, and, of 48 cases of sclerosis of the retinal arterioles, Grade 3 to 4, 86% had a ratio of less than 1.4. Again,

of 34 patients with mean ratios of lumen-to-wall greater than 1.3 of the arterioles of muscles, 50% were dead in 2 years, although of 98 cases, in which the mean ratios of lumen-to-wall were 1 to 1.3, 70% were dead in 2 years and, of 6 patients who had ratios less than 1, all were dead in 2 years.

TABLE 2.—RATIOS OF LUMEN-TO-WALL, ARTERIOLES OF MUSCLE.

Hyper-tension, group.	Total patients.	Ratio of lumen-to-wall.		
		Maximum.	Minimum.	Mean.
1	10	1.8	1.3	1.7
2	26	1.9	0.8	1.3
3	37	2.0	1.0	1.3
4	65	1.8	0.9	1.2

TABLE 3.—QUALITATIVE CHANGES IN ARTERIOLES OF MUSCLE.

Hyper-tension, group.	Total patients.	Definite proliferation of intima, patients.	Patients.		Any qualitative changes present.	
			Organ-ized throm-bosis.	Arter-itis, peri-arteritis.	Total patients.	Per cent of total patients.
1	10	1	0	0	1	10
2	26	11	1	2	11*	42
3	37	6	4	1	10*	28
4	65	22	9	3	31*	48

* In some cases, more than one type of change was found.

Prognosis. The outlook for patients who have essential hypertension affords a striking example of the variableness of processes of the disease. The present series of cases offers a good control for

TABLE 4.—PATIENTS ALIVE 5 TO 9 YEARS AFTER FIRST EXAMINATION.

Hyper-tension, group.	Total patients.	Patients alive.		
		Male.	Female.	Total.
1	10	4	2	6
2	26	4	5	9
3	37	2	1	3
4	146	0	1	1*
Total	219	10	9	19

* This patient was alive 11 years after first examination.

TABLE 5.—PATIENTS DEAD 5 TO 9 YEARS AFTER FIRST EXAMINATION.

Hyper-tension, group.	Total patients.	Patients dead.		
		Men.	Women.	Total.
1	10	3	1	4
2	26	10	7	17
3	37	20	14	34
4	146	99	46	145
Total	219	132	68	200

any specific form of therapy as treatment consisted of general measures, especially with regard to diet and rest and the regular use of certain sedatives. If the fact is considered that only 19 patients, or 9% of our entire series of 219, were alive 5 to 9 years after the

diagnosis was made, the seriousness of the prognosis for all patients seems obvious. But, on further analysis, this grave outlook is more apparent than real, as a disproportionate number of the cases belonged in Group 4. There are some patients in each group and as many as 35 to 60% in Groups 2 and 1 that are alive for a similar period of 5 to 9 years. These facts emphasize the significance of the original grouping particularly from the prognostic standpoint and also demonstrate that there are two predominating types of essential hypertension, the relatively stationary or benign and the rapidly progressive or malignant (Tables 4 and 5).

TABLE 6.—DEATH AT YEARLY INTERVALS AFTER FIRST EXAMINATION.

Years.	Per cent.			
	Group 1.	Group 2.	Group 3.	Group 4.
1	10	12	35	79
2	20	23	67	88
3	30	38	78	94
4	30	42	78	98
5	30	46	80	99

TABLE 7.—DURATION OF LIFE AFTER FIRST EXAMINATION.

Group.	Total patients.	Duration of life, months.	
		Median.*	Mean.†
1	10	100.0	
2	26	63.0	
3	37	15.9	27.6
4	146	5.4	10.5

* The time in months after first examination during which 50% of the patients in the group have died.

† The mean duration of life after first examination. Can be calculated only for the groups, practically all the patients of which have died; that is, Group 3 and Group 4.

The prognosis for cases of Group 3 and, especially, for cases of Group 4 is very serious. Because many more males than females belong to these two groups, the death rate is much higher among males than among females. A death rate, within 1 year, of 35%, in cases of Group 3, and 79%, in cases belonging to Group 4, is in distinct contrast with that of 10 to 12% in Groups 1 and 2. The mortality rate in cases of Group 4 approaches that found in certain forms of cancer (Table 6). In order to emphasize the difference in prognosis of the individual groups, survival curves as employed by statisticians were drawn* (Table 7; Fig. 1). The resulting curves are distinct for each of the four groups. As might be expected, there is a gradual increase in the steepness of the curves from that of Group 1 to that of Group 4. These statistical findings give further support to the conception that there are different types of essential hypertension.

* The authors are indebted to our statistician, Dr. J. Berkson, for making the necessary calculations for this table and chart.

Comment. In the present attempt to group cases of essential hypertension clinically, we realize that not all cases fall into one of the four groups mentioned. There are many patients who have this condition who have, in addition to arteriolar dysfunction, diffuse arteriosclerosis, more especially of the aorta and of the coronary and cerebral arteries. Atherosclerosis of these arteries may be the determining factor as to the course and prognosis. With more knowledge relative to the occurrence of atherosclerosis in such vital internal arteries and with the aid of more accurate diagnostic methods, these cases might be grouped in a much more satisfactory manner than is possible at present.

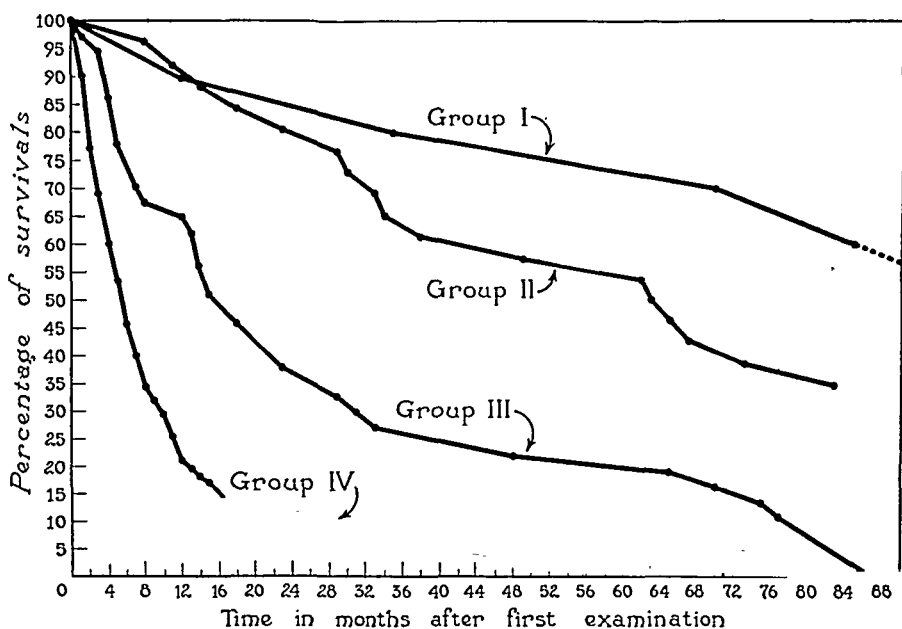


FIG. 1.—Survival curves in the four groups.

All students of the problem of essential hypertension are agreed that arteriolar dysfunction plays an important rôle in perpetuating the condition. Because the arterioles are small and are difficult to visualize in the peripheral organs, for example in the skin, mucous membranes, and voluntary muscle, the retina, as seen through the ophthalmoscope, offers a unique opportunity for observing these small vessels clinically from time to time. Therefore, we think that certain visible changes of the retinal arterioles have been of exceptional value in affording a clearer clinical conception of altered arteriolar function throughout the body. In the present grouping, the retinal observations occupy an important place. Technical difficulties still prevent satisfactory optical examination of arterioles in other living human tissues but, as these are gradually eliminated

in the human being, as they have been by Clark and his coworkers² in their study of the vessels in the rabbit's ear, it will be most interesting to compare findings obtained in such a manner with those in the retina. Our histologic study of the arterioles in muscle was an attempt to obtain somewhat similar information, particularly as to the presence or absence of pathologic change. Functional changes, of course, could not be estimated by such a technique.

We are fully cognizant of the limitations of the study of arterioles in muscle obtained by biopsy, in supplying important clinical data concerning the patient. Naturally, biopsy of muscle permits study of only a small sample of the general arteriolar bed of the body. There is also a certain personal equation in the examination of biopsy specimens. The biopsied muscles, however, in our series of cases were all examined by one of us who did not know anything about the type of hypertensive disease present. Although the changes in the arterioles are never great, they are definite to one who has had some experience in examining these specimens. In many instances, the changes in the arterioles are quite uniform throughout. In others, there is a great deal of variation, normal and markedly constricted arterioles being seen side by side. It is our opinion that definite organic changes in the arterioles of striated muscle usually are found in the more severe cases of hypertensive disease. Their absence, in some cases, and their extreme variability, in others, is evidence that they are secondary or, at the most, are concomitant changes as compared with generalized arteriolar spasm which most probably is the chief mechanism of hypertension. Possibly, the failure to find the organic changes in some cases of otherwise severe hypertensive disease, particularly in those of Group 4, is explained by the fact that the disease has been very rapidly progressive. Because similar, although usually more marked changes frequently are found in the arterioles of the kidney, choroid, and retina, it is probable that the arterioles in different parts of the body may be affected by organic change fairly uniformly in some cases although, in others, organic involvement may be very patchy. This is an argument in favor of the concept that vascular tissue, in some cases, may have a variable vulnerability in different organs and tissues.

It is quite evident that an important problem among these patients is the variation in the clinical course, length of life, and the pathologic lesions. Janeway⁶ emphasized this point in his series of cases in 1913. This variation must be due to several factors. The apparent ones are the inherent condition of the elements composing the arterial and arteriolar wall, alteration of the nervous stimuli to arteries and arterioles, and the adaptability of the cardiovascular system as a whole. The various components of the latter obviously are exposed to abnormal stimuli and to excessive strain. It is still

not clear why, in some cases, the function of a single vital organ fails before others, or why, in some, several important organs cease to function simultaneously.

Goldblatt and his co-workers⁵ experimental production of chronic hypertension by curtailing the arterial blood supply to the kidneys naturally has revived the conception of both Volhard¹⁶ and Fahr^{3b} that essential hypertension is primarily attributable to renal dysfunction. There are many cases, however, that cannot be explained satisfactorily on such a hypothesis, as, for example, those cases associated with tumors of the adrenal and pituitary glands. It seems more logical to assume that there are several causes of hypertension, and as these factors become more clearly defined, clinical cases will be classified on an etiologic basis. In the meantime, accurate studies of the physiologic status and clinical course of the individual patient will lead to better grouping of the cases and, therefore, to a more accurate approach to the therapeutic problem of hypertension.

Summary. A study of 200 cases of essential hypertension revealed a constant abnormal factor; namely, excessive narrowing of the arterioles whether it be due to histologic change or increased vasoconstriction. The findings of previous investigators that there is a marked variation in the clinical course, length of life and pathologic lesions have been confirmed. The clinical subdivision of our cases into four groups has permitted an intelligent appraisal of the individual patient and has increased considerably the accuracy of prognosis. Furthermore, the statistical finding of a distinct survival curve for each of the groups adds support to the viewpoint that distinct types of essential hypertension can be differentiated clinically.

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THE POSTMORTEM WEIGHT OF THE "NORMAL" HUMAN SPLEEN AT DIFFERENT AGES.

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IN connection with a study* of the ageing process in lymphatic tissue, it became desirable to have figures for the weight of the human spleen and its content of lymphatic tissue at different ages—data based on a larger material and extending over a greater period of the life span than are now available. This and a paper recently published³ are the result of these studies.

The human spleen has notoriously the widest range of so-called "normal" weight of any of the important viscera, so that the frequently accepted "normals" of 150 to 200 gm. mean even less here than they do for other organs.

As might be expected, considerable differences may be found in the literature, ranging from Neugarten's⁷ (1921) average normal of 115 gm. to Hyrtl's⁴ (1846) 250 to 300 gm. Vierordt¹⁰ (1893) tabulates 298 male and 305 female spleen weights divided into 36 groups between birth and 25 years. The weights given by him (combined for both sexes) rise from 10.7 gm. at birth to a maximum of 168.3 gm. at 25 years, the most marked rise occurring about the age of 15, with the males' spleens (after the first 2 years) weighing slightly more than the females'.

Lubarsch⁵ (1926) has tabulated spleen weights for both sexes in 11 groups between birth and 40 years. There were 484 females and 541 males (total, 1025), selected from the Charité Hospital on the basis that the spleen showed no noteworthy structural changes. Starting at 9.5 gm. as the spleen weight at birth for both sexes, the weights increased, with no significant differences between sexes, to 77 gm. for the 10 to 15 age group, 121 gm. at 15 to 20, 144 gm. at 20 to 30, and 144 gm. for 30 to 40. He regards 150 gm. as an average postmortem weight for the normal adult spleen. In 569 males and 233 females (total, 802), selected on the same basis by Rössle and Roulet⁹ (1932), somewhat similar figures were obtained. Starting with the weights of 11.2 and 10.2 gm. at birth, the weights rose steadily to a maximum for males of 169.1 gm. in the third decade and for females of 153.7 in the fourth decade. From then on, their spleen weights decreased with increasing age, averaging near 112 gm. in the seventh decade, and near 103 gm. for all persons

* Chapter on Lymphatic Tissue in "Problems of Ageing" edited by E. V. Cowdry. Baltimore, Williams & Wilkins, 1939.

over 70. Two spleens over 90 years of age averaged 65 gm. Though the authors state that they found no constant or decisive ("durchgehenden") difference between the sexes, their figures show greater weights for the male, as high as 25%, in all but 6 of the 30 age groups studied. Neugarten (1921), on the other hand, found an average weight for males in the 25 to 40 age group of 113.3 gm. as compared to 140 gm. for females. However, Moon⁶ (1928) and Ahronheim¹ (1937), like ourselves, found slightly but consistently smaller figures for the female than the male spleens. Pearl and Bacon⁸ (1921-1924) found that the spleen increased in weight up to the 35-year period, after which it progressively declined. They computed from Oppenheimer's (1889) accidental deaths, that at 25 years the male spleen averaged 164.8 gm., the female 160.7 gm. In Moon's (1928) 2000 cases above 18 years of age, from the Philadelphia General Hospital before 1928, the spleen weight decreased progressively in each of the 8 decades studied.

Even Lubarsch's material is none too large when scattered over 11 age groups and his figures stop at the fortieth year, just when the changes of older life should be most intensively sought after. Rössle and Roulet's figures also do not cover the older age periods in desirable amplitude, and in neither was there any analysis of the types of disease met in the different age groups.

Method. Necessarily limited to postmortem material, we have collected our data in two main groups: 1, From persons dying from miscellaneous diseases; 2, from persons dying violent deaths. The first half of the study was based on the records in this department from autopsies made at the University Hospital and at the Philadelphia General Hospital after 1928. Protocols including body weight, spleen weight, anatomic diagnoses and description of spleen were available. Most of the cases came from the general hospital where there is a large number of chronic cases (tuberculosis and others). Working back from those most recently completed, suitable cases were listed by color and sex in 18 semi-decades (from birth to 80 years and over in the last group) until 2000 cases were assembled.

Following the method adopted by Lubarsch, no spleens that had noteworthy lesions were included. This was a simple matter when such conditions as leukemia, Hodgkin's disease, malaria, typhoid, infarcts, amyloid spleen, splenic tuberculosis, and so on, were met. Difficulty was, however, encountered with the borderline lesions such as "acute splenic tumor," which varies from a considerable enlargement to an insignificant change appearing in many febrile deaths. It is well known that the spleen appears in the anatomic diagnosis at autopsy more frequently than any organ in the body and usually with such diagnoses as congestion, or cellular hyperplasia. These, then, if inconsiderable in degree, had to be included if such a study was to be made at all, though it was recognized that the

results could not be interpreted as "normal" spleen weights. Arbitrarily all spleens weighing over 300 gm. were discarded, except where, as was occasionally the case, a spleen above 300 gm. had been shown to be "normal" to gross and microscopic examination.

Body weights (accurate to less than 1 kilo) were also listed, so that the relative as well as the absolute weights of the spleen could be compared for the sexes and blacks and whites at different age periods. If one assumes that in a given age group normal individuals' spleen weights should bear approximately the same proportion to the body weight, it was thought possible that some of the deviations of the mean spleen weights at different periods could be explained in this way; *e. g.*, a high mean spleen weight in a given age group would be accounted for if there was a corresponding high body weight. It was hoped, also, that sufficient information could be obtained about the nationalities of the subjects to indicate whether they would show any trend in spleen weights, such as the relatively lighter weight of the negro's spleen; but it did not prove possible to obtain sufficient reliable figures on this point to permit satisfactory analysis.

The recorded chief cause of death and the condition of the spleen were listed and these were made the basis of an analysis (by S. W. L.) which, as far as we know, has not been previously attempted, in an effort to group these causes into categories in each of which the effect on the spleen was more or less similar. It was hoped that this also might elucidate irregularities found in the mean curve of spleen weights. Thus a peak in a given age group, whether or not affected by an irregularity in the mean body weight in the same group, might be partly explained, let us say, by an increased number of acute infectious deaths or other conditions increasing the weight of the spleen in that group, or similarly a depression in spleen weight attributable to, let us say, an abundance of wasting disease in a given group.

It was found desirable to construct 18 groups (Table 3), which, while having neither a purely etiologic nor morbid anatomic basis of classification, were devised to group together conditions resulting from inflammatory, circulatory, neoplastic processes and the like (with a few necessary subdivisions) that would be expected to have similar effects on spleen weight. Obviously an individual might have a combination of diseases of which one must be selected for listing. For instance, a patient with paralysis agitans and bronchopneumonia would be listed in the latter category, as it would more definitely affect the final spleen weight. As a further example, in the case of malignant disease complicated by bronchopneumonia, if the latter was thought to have had a predominant effect on the spleen, it would be the one listed.

The first group includes those cases where congenital lesions were thought to have the predominant effect on the spleen (representing

1.3%). Next, metabolic and endocrine disorders include mostly such conditions as malnutrition and marasmus in infants, and in the older group, diabetes mellitus, Graves' disease, and so on (totalling 3.2%). The blood diseases include only those of the so-called primary type (0.79%). Hemorrhage (3.7%) includes frank hemorrhage, such as occurs from an ulcer in a hollow viscus, in contrast to thrombosis and embolism (5%), which also includes cerebral hemorrhage. The arteriosclerosis group (6.3%) is self-evident. The acute respiratory infections (21.7%) are made up chiefly of the various pneumonias; while the acute gastro-intestinal diseases (3.7%) include such conditions as appendicitis and enteritis. Acute cardiovascular diseases (1.9%) are obvious, while acute other conditions (5.7%) include septicemia and miscellaneous acute disorders. The large chronic respiratory group (9.1%) is made up mostly of fibrocaceous, ulcerative tuberculosis (including acute exacerbations). Close to it in importance are the chronic cardiovascular diseases (7.6%), mostly of luetic and rheumatic etiology. In the next group, are other chronic states not included elsewhere (3.3%). Non-infectious cardiovascular renal and liver diseases (5.7%) are exemplified by such conditions as nephrosclerosis and toxic liver necroses. Malignant tumors (12.9%) rank second in importance to acute respiratory disease. Nervous diseases (1.3%) include both acute and chronic organic lesions, central and peripheral. Finally, all cases not fitting in the above arbitrary divisions fall into the miscellaneous section (8%). (See Table 3 for age distribution.)

Recognizing the shortcomings of statistics based on disease deaths, we have succeeded in also obtaining data on another series of 2000 spleen and body weights in cases of death from all kinds of violence, especially of those cases dying shortly after the violence and uncomplicated by infection or known accompanying disease.* They have been divided into the same 18 age periods as in the disease group. As it appeared that analysis according to sex and color would not contribute anything beyond that made on the first group, it was not carried out for the violent deaths. It was hoped, at first, that the spleens of this series might be regarded as "supposedly normal"

* Our heartiest thanks are given to the Medical Examiners and Coroner's physicians of Boston, New York and Philadelphia, whose generous coöperation alone made this study possible. Dr. Leary in Boston had a P.W.A. staff of 4 working for 3 months transcribing details of over 1000 cases from his excellent records extending back to 1916. Dr. Helpert, of the Manhattan Medical Examiner's Office, was equally helpful with tissues and records of over 1000 cases, while Dr. Werne, at the Jamaica, L. I., office, was most generous with the records and slides under his control. Dr. Crane and the other Coroner's physicians of Philadelphia kindly gave us records and tissues over many months as the cases were autopsied, though records of previous cases here were not available. In all the autopsy rooms the organs were weighed on scales in good working order. These were accurate to 5 gm., though the important factor of loss of splenic blood after death and after excision of the organ at autopsy could not be accounted for. The body weights represent actual weighings (except in one morgue where they were estimated by one person, practised over many years, and probably represent an accuracy of within 4 or 5 kilos).

spleens, but it soon became evident that two factors tending to decrease the weight of the spleen—hemorrhage and shock—could not be excluded, both because of their frequency and because of inconstant recording of such features and inability to give quantitative estimates. As both these phenomena tend to cause blood to be squeezed from the splenic reservoir, it is obvious that the mean weights for this group should be somewhat below normal. It was found, however, that averages obtained with shock and hemorrhage cases excluded as far as possible were only a few grams higher for most age groups than when such cases were included. In fact, in a few age groups, the hemorrhage and shock spleens averaged even higher weights than the general mean for that group.

Another factor that may interfere with the normalcy of the spleen weight in violent deaths is the length of time occurring between the violence and death. Though all cases were excluded when the spleen was noted as in any way abnormal, and less than a dozen included where there was any evidence in the body of complicating sepsis or even a terminal infection, yet the survival period was frequently not given, some lived more than a day or even a week or longer. Thus of 731 cases in which the survival period was known, 81 % died within 24 hours, and 11 persons lived for more than a week after the violence. We do not believe, however, that this disturbing factor has materially influenced the mean values presented.

Analysis of the causes of the 2000 violent deaths is hampered by the different criteria used by the various pathologists—some indicating the type of violence, others the anatomic results and still others, both. Nor is it important to our main purpose that these be minutely classified. However, in general, it may be said that fractured skull—the commonest cause of death—was noted in 492 cases, of which 121 were specified as due to an automobile accident and doubtless many others were due to the same cause. All other fractures were responsible for 146 cases. "Multiple injuries" caused 241 deaths, of which 191 were listed as due to automobile accidents. We estimate that the automobile was responsible for about 25 % of the total. This percentage is less than the 39.3 % in the Metropolitan Life Insurance Company's figures (Dublin and Lotka²), which we have selected as a good basis for comparison. There were 305 deaths from gunshot wounds, 15.2 % (as compared with 2.5 % of the Metropolitan), and 179 from cuts and stab wounds. Excepting carbon monoxide poisoning (78 cases) and acute alcoholism (listed as the primary cause in 45 cases), poisons accounted for 123 cases. These were of 16 kinds, the most numerous being a score of cyanide cases. There were 75 deaths listed as due to falls, 61 to asphyxia, 42 drowned, 28 hanged or strangled, 49 to ruptured viscera, 48 crushed, 22 burned, and 66 from miscellaneous causes.

The fact that the curve of "violent" spleen weights is significantly lower than the "disease" curve indicates that the material of the

two groups is truly different, and yet the remarkable parallelism found in the details of the two curves suggest that neither is far from the true normal.

Finally, as the "disease" cases of the first group tended, in our opinion, to have spleens slightly heavier than the true normal, and the "violent" cases of the second group slightly lighter than normal, it was thought that combination of the spleen weights in all 4000 cases would give a curve for the different age periods that should be nearer the true normal than either of the individual groups (Chart 1).

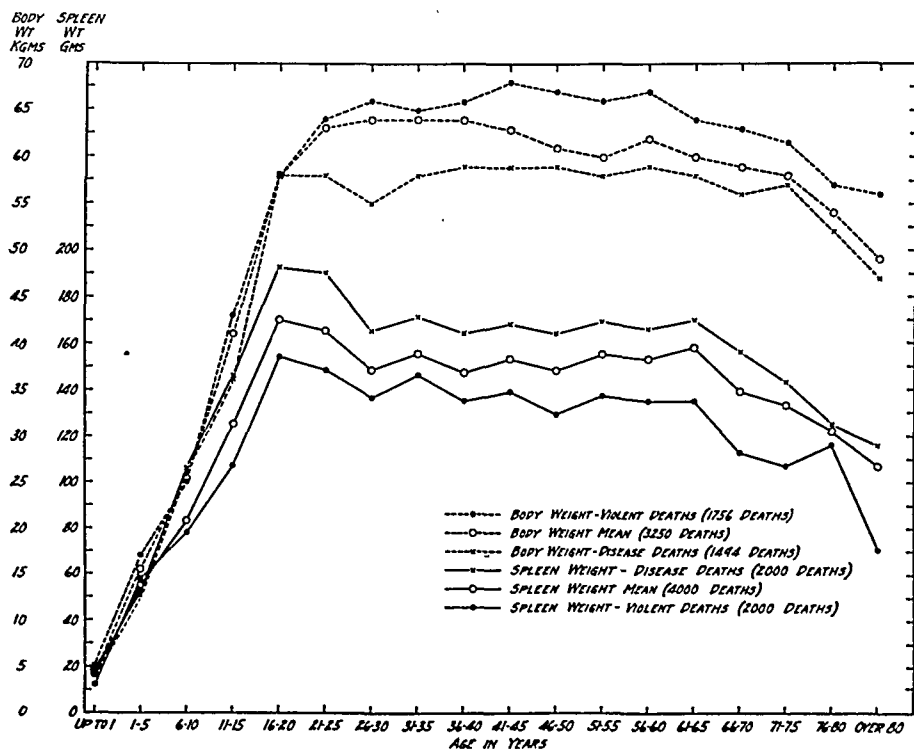


CHART 1.—Mean spleen and body weights at different age periods (4000 cases).

It is obvious, then, that this material, though similar in quality to that of other workers in the field, is far from ideal. Its value is limited by the many sources from which it is drawn, as well as by unknown or uncontrollable variables, and solace must be taken in the safety that exists in large numbers.

Results. The results of the "disease" group study (Tables 1 and 2; shown graphically in the uppermost and fourth curves of Chart 1) gave distinctly higher spleen and body weights in this series than in the German studies. Also the maximum weight was reached earlier in life. Statistical analysis showed that the 16 to 20 and 21 to 25 age groups had significantly heavier spleens than any

TABLE 1.—SPLEEN WEIGHTS AT DIFFERENT AGES (2000 "DISEASE" DEATHS).

Age (yrs.).	Male white.			Female white.			Female black.			White.			Black.			Male.			Female.		
	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.
	2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.	
Up to 1	19.9 ± 4.8	14.7 ± 4.6	29	17.5 ± 3.4	19.4 ± 11.2	88	18.7 ± 4.2	16.0 ± 14.6	49	10.6 ± 5.8	72	10.6 ± 5.8	50 ± 10	50 ± 10	65	18.1 ± 8.6	49 ± 10.4	65	18.1 ± 8.6	49 ± 10.4	65
1-5	54 ± 14.6	57.5 ± 14.2	16	51 ± 13.8	45 ± 10.2	34	53 ± 10.2	50 ± 10	10	53 ± 10.2	22	55 ± 10.2	120 ± 72	120 ± 72	6	121 ± 58	121 ± 58	6	121 ± 58	121 ± 58	6
6-10	88 ± 8.6	80 ± 7.2	3	121 ± 60	95 ± 8.2	13	103 ± 34	89 ± 14	3	103 ± 34	20	97.5 ± 36	109 ± 34	109 ± 34	17	159 ± 50	159 ± 50	17	159 ± 50	159 ± 50	17
11-15	140 ± 36	120 ± 28	2	173 ± 30	172 ± 46	32	155 ± 34	167.5 ± 32	31	155 ± 34	36	134 ± 35	167.5 ± 32	167.5 ± 32	37	169 ± 27	169 ± 27	37	169 ± 27	169 ± 27	37
16-20	237 ± 44	161 ± 46	13	166 ± 30	152 ± 22	48	209 ± 21	173 ± 21	59	209 ± 21	57	202 ± 24	173 ± 21	173 ± 21	50	175 ± 27	175 ± 27	50	175 ± 27	175 ± 27	50
21-25	231 ± 29	189 ± 31	25	199 ± 39	141 ± 39	24	186 ± 22	138 ± 20	44	186 ± 22	48	197 ± 24	138 ± 20	138 ± 20	48	152 ± 17	152 ± 17	48	152 ± 17	152 ± 17	48
26-30	293 ± 30	207 ± 40	26	166 ± 26	141 ± 34	30	192 ± 22	135 ± 24	38	192 ± 22	57	180 ± 23	135 ± 24	135 ± 24	44	161 ± 24	161 ± 24	44	161 ± 24	161 ± 24	44
31-35	377 ± 30	287 ± 28	20	175 ± 24	134 ± 31	18	157 ± 26	108 ± 24	15	157 ± 26	86	179 ± 18.6	108 ± 24	108 ± 24	65	174 ± 22	174 ± 22	65	174 ± 22	174 ± 22	65
36-40	392 ± 34	335 ± 24	30	153 ± 24	157 ± 36	100	179 ± 17.4	150 ± 24	56	179 ± 17.4	86	179 ± 18.6	150 ± 24	150 ± 24	70	174 ± 22	174 ± 22	70	174 ± 22	174 ± 22	70
41-45	587 ± 24	443 ± 34	24	184 ± 28	131 ± 36	142	176 ± 15.8	128 ± 20	4	176 ± 15.8	32	126 ± 22	128 ± 20	128 ± 20	12	133 ± 30	133 ± 30	12	133 ± 30	133 ± 30	12
46-50	1027 ± 15.8	126 ± 34	20	191 ± 28	120 ± 30	137	185 ± 15	128 ± 20	4	185 ± 15	128 ± 20	126 ± 22	128 ± 20	128 ± 20	65	159 ± 24	159 ± 24	65	159 ± 24	159 ± 24	65
51-55	98185 ± 17.4	127 ± 22	23	183 ± 38	102 ± 30	102	185 ± 15	128 ± 20	4	185 ± 15	128 ± 20	126 ± 22	128 ± 20	128 ± 20	65	159 ± 24	159 ± 24	65	159 ± 24	159 ± 24	65
56-60	92180 ± 20	169 ± 22	34	158 ± 32	88 ± 24	142	182 ± 18.2	138 ± 22	15	182 ± 18.2	86	179 ± 17.6	138 ± 22	138 ± 22	63	145 ± 26	145 ± 26	63	145 ± 26	145 ± 26	63
61-65	91192 ± 16	135 ± 28	20	161 ± 24	106 ± 32	13	151 ± 15.8	102 ± 30	15	151 ± 15.8	86	179 ± 17.6	102 ± 30	102 ± 30	63	149 ± 22	149 ± 22	63	149 ± 22	149 ± 22	63
66-70	78170 ± 19.2	167 ± 28	10	138 ± 18	92 ± 22	94	151 ± 15.8	102 ± 30	15	151 ± 15.8	86	179 ± 17.6	102 ± 30	102 ± 30	63	149 ± 22	149 ± 22	63	149 ± 22	149 ± 22	63
71-75	54153 ± 17	99 ± 32	5	141 ± 20	60 ± 60	54	128 ± 15.8	93 ± 40	4	128 ± 15.8	32	126 ± 22	93 ± 40	93 ± 40	21	133 ± 30	133 ± 30	21	133 ± 30	133 ± 30	21
76-80	34123 ± 24	110 ± 64	2	136 ± 32	70 ± 14.2	40	119 ± 20	93 ± 40	4	119 ± 20	32	126 ± 22	93 ± 40	93 ± 40	12	91 ± 18	91 ± 18	12	91 ± 18	91 ± 18	12
Over 80	30127 ± 24	115 ± 64	10	95 ± 42	70 ± 14.2	40	119 ± 20	93 ± 40	4	119 ± 20	32	126 ± 22	93 ± 40	93 ± 40	12	91 ± 18	91 ± 18	12	91 ± 18	91 ± 18	12

(350)

TABLE 2.—BODY WEIGHTS AT DIFFERENT AGES ("DISEASE" DEATHS).

Age (yrs.).	Male white.			Male black.			Female white.			Female black.			White.			Black.			Male.			Female.		
	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.	Mean.		No.
	2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.		2SE.	2SE.	
Up to 1	4.8 ± 0.7	3.4 ± 0.6	21	4 ± 0.8	3.2 ± 0.8	17	4.4 ± 0.3	3.3 ± 0.1	38	4.4 ± 0.3	56	4.3 ± 0.3	3.3 ± 0.1	3.3 ± 0.1	50	3.7 ± 0.2	3.7 ± 0.2	50	3.7 ± 0.2	3.7 ± 0.2	50	3.7 ± 0.2	3.7 ± 0.2	50
1-5	11.5 ± 2.8	14 ± 0.7	11	13.9 ± 4	11 ± 1.4	0	12.8 ± 2.6	12 ± 1.8	3	12.8 ± 2.6	12	11.7 ± 2.6	12 ± 1.8	12 ± 1.8	15	13.5 ± 3.6	13.5 ± 3.6	15	13.5 ± 3.6	13.5 ± 3.6	15	13.5 ± 3.6	13.5 ± 3.6	15
6-10	24.3 ± 2.8	21.5 ± 0.7	2	34 ± 7	43 ± 7	0	28.2 ± 5.4	21.5 ± 0.7	2	28.2 ± 5.4	5	23.2 ± 2.2	21.5 ± 0.7	21.5 ± 0.7	2	34 ± 7	34 ± 7	2	34 ± 7	34 ± 7	2	34 ± 7	34 ± 7	2
11-15	34.5 ± 7	22 ± 5	13	55 ± 6.2	78 ± 9.2	1	36 ± 5.2	43 ± 6	1	36 ± 5.2	6	34.5 ± 7	43 ± 6	43 ± 6	10	39.1 ± 8.8	39.1 ± 8.8	10	39.1 ± 8.8	39.1 ± 8.8	10	39.1 ± 8.8	39.1 ± 8.8	10
16-20	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
21-25	65 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
26-30	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
31-35	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
36-40	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
41-45	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
46-50	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
51-55	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
56-60	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
61-65	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
66-70	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
71-75	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
76-80	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13
Over 80	55 ± 6.2	22 ± 5	1	53 ± 4.9	49 ± 5.6	5	54.5 ± 4.2	53 ± 4.9	6	54.5 ± 4.2	4	53 ± 4.9	53 ± 4.9	53 ± 4.9	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13	63 ± 8.2	63 ± 8.2	13

other group. The lower spleen weight level of the 26 to 30 age group was maintained with but little change to the 65th year; application of the regression coefficient indicates that in this section the line is the equivalent of a horizontal one. The maintenance of the spleen

TABLE 3.—ANALYSIS OF 2000 "DISEASE" CASES AS TO CAUSE OF DEATH.

Age (yrs.).	Congenital.	Metabolic and endocrine.	Blood diseases.	Hemorrhage.	Thrombosis and embolism.	Arteriosclerosis.	Acute respiratory.	Acute cardiovascular.	Acute gastro-intestinal.	Acute other conditions.	Chronic respiratory.	Chronic cardiovascular.	Chronic other conditions.	Non-infectious cardiovascular renal and liver diseases.	Tumors.	Nervous.	Miscellaneous.	Total.
Up to 1 year																		
No. of cases	21	39	1	9	35	..	1	8	3	..	7	..	2	..	11	137
Per cent	15.5	28.5	0.7	6.6	25.6	..	0.7	5.8	2.2	..	5.1	..	1.5	..	8.0	6.85
1-5																		
No. of cases	2	1	..	12	2	6	6	4	1	4	..	1	2	3	44
Per cent	4.5	2.3	..	27.3	4.5	13.6	13.6	9.1	2.3	9.1	..	2.3	4.5	6.8	2.20
6-10																		
No. of cases	1	8	..	1	3	..	1	2	16
Per cent	6.2	50.0	..	6.2	15.8	..	6.2	12.5	0.80
11-15																		
No. of cases	1	2	2	1	1	3	2	4	4	4	4	3	6	37
Per cent	2.7	5.4	5.4	2.7	2.7	8.1	5.4	10.8	10.8	10.8	10.8	8.1	16.2	1.85
16-20																		
No. of cases	..	1	..	3	11	2	3	4	24	5	2	2	5	2	9	73
Per cent	..	1.4	..	4.1	15.0	2.7	4.1	5.5	32.0	6.8	2.7	2.7	6.8	2.7	12.3	3.65
21-25																		
No. of cases	..	1	1	1	21	1	3	9	43	2	1	4	4	1	15	107
Per cent	..	0.9	0.9	0.9	19.6	0.9	2.8	7.4	40.0	1.9	0.9	3.7	3.7	0.9	14.0	5.35
26-30																		
No. of cases	..	2	3	1	23	3	5	10	12	13	4	9	7	1	3	96
Per cent	..	2.1	3.2	1.0	24.0	3.2	5.2	10.4	12.5	13.5	4.2	9.4	7.3	1.0	3.2	4.80
31-35																		
No. of cases	..	2	..	5	20	5	5	7	15	15	2	6	9	..	10	101
Per cent	..	2.0	..	5.0	19.8	5.0	5.0	6.9	14.8	14.8	2.0	5.9	8.9	..	9.9	5.05
36-40																		
No. of cases	..	3	2	10	7	..	34	1	5	12	15	16	3	5	24	1	13	151
Per cent	..	2.0	1.3	6.6	4.1	..	22.5	0.7	3.3	7.9	9.0	10.6	2.0	3.3	15.9	0.7	8.6	7.55
41-45																		
No. of cases	..	1	..	12	9	1	37	4	9	7	12	18	10	12	11	4	8	155
Per cent	..	0.6	..	7.7	5.8	0.6	23.9	2.6	5.8	4.5	7.7	11.6	6.4	7.3	7.1	2.6	5.2	7.75
46-50																		
No. of cases	..	2	1	10	14	2	40	2	4	10	8	16	6	10	32	6	24	187
Per cent	..	1.1	0.5	5.3	7.5	1.1	21.4	1.1	2.1	5.3	4.3	8.5	3.2	5.3	17.1	3.2	12.8	9.35
51-55																		
No. of cases	..	2	1	11	17	5	37	4	7	5	12	20	4	12	45	..	7	189
Per cent	..	1.1	0.5	5.8	9.0	2.6	19.6	2.1	3.2	2.6	6.4	10.6	2.1	6.4	23.8	..	3.7	9.45
56-60																		
No. of cases	..	4	1	4	13	18	31	5	6	9	12	16	1	14	33	3	15	185
Per cent	..	2.2	0.5	2.2	7.0	9.7	11.8	2.7	3.2	4.9	6.5	8.6	0.5	7.6	17.8	1.6	8.1	9.25
61-65																		
No. of cases	..	2	2	3	14	21	36	1	6	6	7	11	2	7	40	..	17	175
Per cent	..	1.1	1.1	1.7	8.0	12.0	20.6	0.6	3.4	3.4	4.0	9.1	1.1	4.0	22.9	..	9.7	8.75
66-70																		
No. of cases	..	3	10	21	31	3	4	6	8	8	8	15	8	2	9	136
Per cent	..	2.2	7.3	15.5	22.8	2.2	2.0	4.4	5.9	5.9	5.9	11.0	5.9	1.5	6.6	6.80
71-75																		
No. of cases	1	8	31	22	..	4	2	2	4	3	6	20	..	4	107
Per cent	0.9	7.5	2.9	20.6	..	3.7	1.9	1.9	3.7	2.8	5.6	18.7	..	3.2	5.35
76-80																		
No. of cases	..	1	..	1	2	9	18	1	2	4	3	2	1	3	7	..	6	60
Per cent	..	1.7	..	1.7	3.3	15.0	30.0	1.7	3.3	6.7	5.0	3.3	1.7	5.0	11.7	..	10.0	3.00
Over 80																		
No. of cases	1	..	3	16	15	3	1	2	3	44
Per cent	2.3	..	6.8	36.3	34.1	6.8	2.3	4.5	6.8	2.20
Total																		
No. of cases	23	63	14	74	98	124	433	35	72	111	182	155	63	117	257	25	169	2000
Per cent	1.2	3.2	0.7	3.7	4.9	6.2	21.6	1.8	3.6	5.6	9.1	7.5	3.2	5.6	12.8	1.2	8.0	

weight up to 65 years, in spite of the tendency to increasing arteriosclerosis and fibrosis of the spleen, might be taken as indirect support for the hypothesis that has been advanced that there is an increase of lymphatic tissue in older middle life. This question is considered in more detail in our second paper in this study (*Am. Jour. Path.*). After 65 years, there occurred a sharp and statistically significant loss of both spleen and body weight.

Analysis of the causes of death, though disappointing on the whole, did bring out a few points (Table 3). For instance, deaths from acute and chronic respiratory diseases were especially prevalent in the 16 to 20 and 21 to 25 age groups. It will be seen later, however, from a similar peak in the violent deaths in the 16 to 20 age group that the respiratory diseases could not be the only factors concerned in placing the heaviest spleen averages in these younger groups. As would be expected, arteriosclerosis became common in the older age groups. While it is obviously a factor to be dealt with in the terminal loss of spleen weight, presumably by damaging the circulation, its importance in the involution of old age cannot as yet be evaluated. The average spleen weight of our 247 tumor spleens between the ages of 16 and 70 was 154 gm., exactly the same as for all our "disease" spleens in those ages. This is in contrast to the tumor spleens in Moon's series, which were lighter than the general average. The 139 spleens of our chronic cardiovascular group averaged, as might be expected, considerably above (179 gm.) the general average for this period. Neither of these comparisons, however, throws any further light on age variations of the "disease" spleen curve.

Analysis of the nine subgroups of the classifications according to sex and color in the 18 age groups of the "disease" cases (Tables 1 and 2) shows that the number of whites and males predominated over that of blacks and females (71 and 59% respectively). In general, female spleens after puberty are lighter than male spleens, and in most groups significantly lighter; also, just as Moon had previously found, the spleens of negroes are significantly lighter than those of whites. (This interpretation is based on the facts that the sex and color differences could not be attributed to differences in mean body weights or to types of disease and on the finding that the differences of the means were more than twice the standard error; in other words, the chances are about 20 in 21 that mean weights from similar material would vary in a similar way.) Moreover, the spleens of whites and blacks show more of a difference than the spleens of males and females. Therefore, it would appear that sex was less of a factor than color. As might be expected, male whites had the heaviest spleens, and negresses the lightest; though the age groups in the negress class often did not have an adequate number of cases.

An analysis of the body weights of the disease group according to sex and color (Table 2) shows less difference among the 8 sub-

groups than do the spleen weights. The male whites were heavier than the blacks in 10 groups, and the males heavier than females in all but 2 groups after the age of 20, but the differences are too slight to be significant, except in a few cases. Unexpectedly, the female whites were heavier than the male blacks in 8 groups, the male blacks heavier in 7. It appears, then, that changes in the spleen weight curve at different age periods cannot be explained by fluctuations in the body weight curve or in their sex or color population. The averaged weight for all adult spleens (16 years or over) was 150.7 gm.; for spleens between the years of 16 and 70, 154 gm.; for all 4000 spleens, 140.7 gm.

Analysis of the histologic appearance of 868 spleens of the disease group (Table 4) shows that 75% were given diagnoses that should be accompanied by a tendency toward increased weight, even though such terms as "congestion" are variably used in routine descriptions and though the cases would not have been included by us if the changes had been marked. Only 2.5% were listed as atrophic. These histologic pictures, then, indicate that the splenic weights in this series of "disease" deaths tend on the whole to be above normal.

In the 2000 cases of violent deaths, analysis of mean spleen and body weights (Tables 5 and 6; 3d and 6th lines of Chart 1) shows that the heaviest spleen weights are attained in the same age group as in the disease groups, though a lower mean weight obtains throughout. The remarkable degree to which the spleen weight curves in the "disease" and the "violent" groups run parallel, has already been mentioned. In the "violent" group, also, where such extraneous factors as high incidence of respiratory or other disease, could not be operative, an early peak was followed by a more level curve, with a terminal drop. As this is more pronounced, however, in the "disease" curve than in the "violent" curve, which has more the appearance of a constant drop from the 16 to 20 age group, this point was investigated for significance statistically, with indecisive results as far as the "violent" curve was concerned. Analysis of the curve of the combined 4000 spleen weights (Table 5; 5th line in Chart 1) indicates clearly that there is a significantly high peak for the two age groups between 16 and 25, an essentially horizontal line for the spleen weights between 26 and 65 years and a significant loss of both spleen and body weight after 65 years.

At face value, these figures would indicate that the human spleen, after reaching a maximum weight soon after puberty, maintains a lower level until about the age of 65, when it again loses weight. If, however, one discounts the effect of the respiratory diseases in the 16 to 25 age groups and remembers the possibility that the "violent" curve may represent a gradual descent through adult life, instead of a hump and a plateau, then one cannot avoid the conclusion that ideal material might perhaps reveal a steady loss of spleen weight after puberty.

TABLE 4.—SPLENIC LESIONS OF CASES FROM TABLE 3.

Age (yrs.).	Congestion.	Infarction.	Atrophy.	Hyperplasia.	Chronic irritations.	Acute splenic tumor.	Miscellaneous.	"Normal."	Total.
Up to 1 yr.									
No. of cases	25	..	4	27	6	1	4	41	108
Per cent	23.1	..	3.7	24.9	5.6	0.9	3.7	37.0	12.45
1-5									
No. of cases	4	3	1	19	2	2	3	5	39
Per cent	10.3	7.7	2.6	8.8	5.1	5.1	7.7	12.8	4.49
6-10									
No. of cases	6	8	1	..	15
Per cent	40.0	53.3	6.7	..	1.72
11-15									
No. of cases	4	1	..	5	..	4	1	..	25
Per cent	56.0	4.0	..	20.0	..	16.0	4.0	..	2.88
16-20									
No. of cases	15	3	1	13	10	4	5	1	52
Per cent	28.8	5.8	1.9	25.0	19.2	7.7	9.6	1.9	5.99
21-25									
No. of cases	24	1	..	19	4	10	1	7	66
Per cent	36.4	1.5	..	28.8	6.1	15.1	1.5	10.6	7.60
26-30									
No. of cases	24	2	1	14	3	8	3	4	59
Per cent	40.7	3.4	1.7	23.7	5.1	13.6	5.1	6.8	6.79
31-35									
No. of cases	22	2	4	11	1	10	2	4	56
Per cent	39.3	3.6	7.1	19.7	1.8	17.9	3.6	7.1	6.45
36-40									
No. of cases	34	2	2	18	6	10	5	4	81
Per cent	43.2	2.5	2.5	22.2	7.4	12.3	6.2	4.9	9.32
41-45									
No. of cases	40	2	2	20	3	12	6	5	90
Per cent	44.0	2.2	2.2	22.2	3.3	13.3	6.7	5.1	10.36
46-50									
No. of cases	33	2	..	12	3	8	5	1	64
Per cent	51.6	3.1	..	18.8	4.7	12.5	7.8	1.6	7.37
51-55									
No. of cases	44	6	..	7	2	9	3	..	71
Per cent	62.0	5.5	..	9.9	2.8	12.7	4.2	..	8.17
56-60									
No. of cases	23	4	4	9	1	3	3	..	47
Per cent	49.0	8.5	8.5	19.2	2.1	6.4	6.4	..	5.41
61-65									
No. of cases	26	6	2	11	..	1	3	..	49
Per cent	53.1	12.3	4.1	22.4	..	2.1	6.1	..	5.61
66-70									
No. of cases	11	1	..	6	18
Per cent	61.1	5.6	..	33.3	2.07
71-75									
No. of cases	12	3	..	4	..	1	20
Per cent	60.0	15.0	..	20.0	..	5.0	2.30
76-80									
No. of cases	4	2	6
Per cent	66.7	33.3	0.69
Over 80									
No. of cases	1	..	1	2
Per cent	50.0	..	50.0	0.23
Total									
No. of cases	362	38	22	205	41	83	45	72	868
Per cent	41.7	4.4	2.5	23.6	4.7	9.6	5.2	8.3	

Study of the ratio of spleen weight to body weight in the 4000 cases (Table 6) shows that it is highest and significantly above subsequent ratios in the earliest age group (0.0042). From then on the slope of the ratio is slightly though not significantly down (from 0.0035 to 0.0022), except for a plateau in the groups between 51

TABLE 5.—SPLEEN WEIGHTS AT DIFFERENT AGES. (COMBINED "DISEASE" AND VIOLENT DEATHS.)

Age (yrs.).	2000 "disease" deaths.			2000 violent deaths.			Total, 4000.		
	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.
Up to 1 yr. . . .	137	17.9 ±	2.2	19	12 ±	3.2	156	17 ±	2.0
1-5	44	52 ±	8.2	71	58 ±	4.4	115	55 ±	4.4
6-10	16	106 ±	30	73	78 ±	7.2	89	83 ±	8.2
11-15	37	146 ±	30	57	107 ±	12.4	94	125 ±	14.4
16-20	73	192.5 ±	23	111	154 ±	12.2	184	170 ±	12.0
21-25	107	190 ±	16	163	148 ±	8.6	270	165 ±	7.6
26-30	96	165 ±	5	214	136 ±	9.2	310	148 ±	7.6
31-35	101	171 ±	17	191	146 ±	9.8	292	155 ±	8.8
36-40	151	164 ±	13.2	209	135 ±	9.2	360	147 ±	7.8
41-45	156	168 ±	14.4	175	139 ±	9.8	331	153 ±	8.6
46-50	191	164 ±	11.8	164	129 ±	9.2	355	148 ±	7.8
51-55	184	169 ±	12.8	142	137 ±	10.6	326	155 ±	8.8
56-60	183	166 ±	14.6	142	135 ±	10.4	325	153 ±	9.6
61-65	175	170 ±	16	102	135 ±	13.4	277	158 ±	11.4
66-70	136	156 ±	13	89	113 ±	12.4	225	139 ±	9.6
71-75	109	143 ±	13.8	43	107 ±	11.6	152	133 ±	10.2
76-80	60	125 ±	14.8	24	116 ±	17.4	84	122 ±	11.6
Over 80	44	116 ±	19.4	11	71 ±	13.2	55	107 ±	16.6

TABLE 6.—BODY WEIGHTS AT DIFFERENT AGES (COMBINED "DISEASE" AND VIOLENT DEATHS).

Age (yrs.).	2000 "disease" deaths.			2000 violent deaths.			Total, 4000.			Ratio of spleen weight to body weight.
	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	
Up to 1 yr. . . .	106	4 ±	0.1	14	5 ±	1.2	120	4.1 ±	0.2	0.0042
1-5	27	12.7 ±	2.2	51	17 ±	1.2	78	15.5 ±	1.2	.0035
6-10	7	26.3 ±	4.4	48	25 ±	2.0	55	25.2 ±	1.8	.0033
11-15	25	36.4 ±	5	48	43 ±	3.6	73	41 ±	3.0	.0030
16-20	27	58 ±	5.8	58	103 ±	2.0	130	58 ±	2.0	.0029
21-25	27	58 ±	4.4	148	64 ±	2.2	175	63 ±	2.0	.0026
26-30	44	55 ±	3.8	200	66 ±	1.8	244	64 ±	1.8	.0023
31-35	32	58 ±	4.6	180	65 ±	1.6	212	64 ±	1.4	.0024
36-40	57	59 ±	4.2	194	66 ±	2.0	251	64 ±	1.8	.0023
41-45	134	59 ±	2.4	141	68 ±	2.8	276	63 ±	1.8	.0024
46-50	176	59 ±	2.6	149	67 ±	2.0	325	61 ±	1.8	.0024
51-55	177	58 ±	2.2	118	66 ±	2.6	295	60 ±	2.8	.0026
56-60	169	59 ±	3.2	125	67 ±	2.2	294	62 ±	2.2	.0025
61-65	158	58 ±	3	88	64 ±	2.6	246	60 ±	2.2	.0026
66-70	127	56 ±	2.6	77	63 ±	4.4	204	59 ±	2.0	.0024
71-75	104	57 ±	3	40	61.5 ±	4.4	144	58 ±	2.6	.0023
76-80	56	52 ±	3	21	57 ±	6.2	77	54 ±	2.8	.0023
Over 80	41	47 ±	3.6	11	56 ±	6.4	52	49 ±	3.2	.0022

and 65 years (0.0026), where the ratio is significantly higher than those of age groups on either side. The ratio of spleen weight to body weight in all ages in the 4000 cases averaged 0.0027. Others have found similar results: the percentage of the spleen weight in the body weight having been found highest from 2 to 7 years (0.32 to 0.39%), falling to about 0.25% at 25 years.

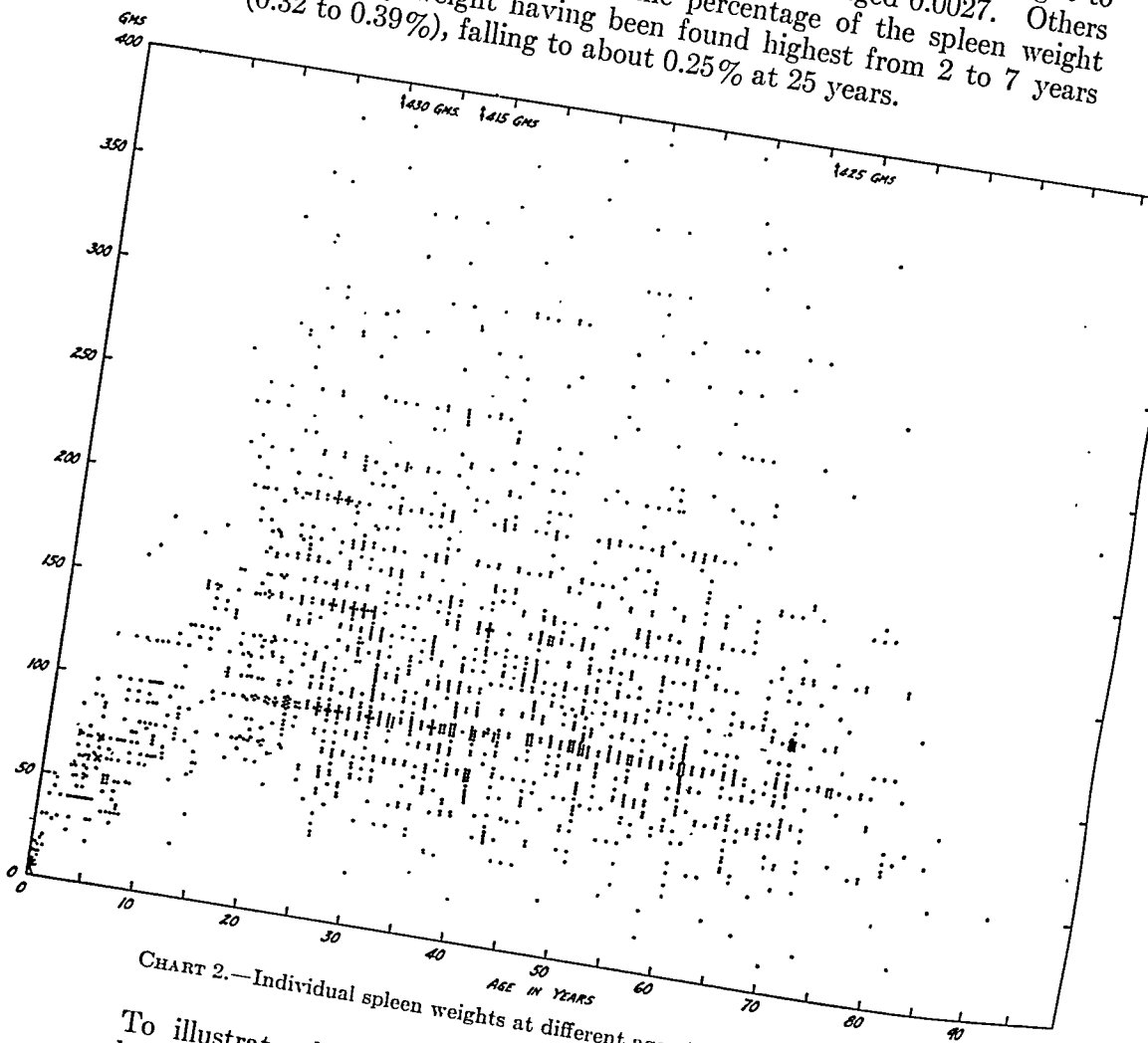


CHART 2.—Individual spleen weights at different ages (2000 violent deaths).

To illustrate the marked "scatter" of supposedly "normal" spleen weights, the individual spleen weights in the group of 2000 violent deaths have been charted (Chart 2). Recalling that these are from persons who from their history and postmortem examination gave no evidence of splenic disease, the deviation from the mean is unexpectedly great in all the age groups. Thus a male white, aged 45, weighing 135 pounds, who committed suicide with cyanide, had a spleen which at autopsy was reported as normal but weighed 400 gm.; a Jewess of 32, weighing 150 pounds, was

strangled—her "normal" spleen was found to weigh 415 gm. At the other extreme, an apparently normal Chinese of 40, weighing 124 pounds, was drowned and his spleen, reported "normal," weighed only 20 gm. Such examples are too numerous to be attributable to error or oversight of pathologic causes. While no explanation is forthcoming for this great variation, it is useful to know that adult spleen weights below 50 gm. or above 400 gm. do not necessarily indicate splenic disease. Weights of apparently normal spleens as low as 100 gm. and as high as 250 gm. are not at all uncommon. It must be emphasized, however, that the term "normal," especially when used by a number of observers, may be subject to considerable latitude of interpretation. Such elements of weakness, however, tend to be minimized by the large number of cases analyzed.

Summary. 1. Postmortem human spleen and body weights have been assembled in 18 age periods (semi-decades, with the last covering all cases over 80 years) in two main groups. In the first group, were studied 2000 cases dying from miscellaneous diseases but without noteworthy involvement of the spleen; in the second group, 2000 cases dying violent deaths.

2. In both of these groups, and therefore in the combined group of 4000 cases, the spleen reached a maximum average weight (170 gm. for the combined group) at the 16 to 20 year period. Between the ages of 26 and 65, the mean spleen weight remained approximately unchanged (155 to 160 gm. for the combined group). After 65 years, it fell markedly, until in very old spleens weights of less than 100 gm. were the rule.

The ratio of the spleen weight to body weight was found to be highest at birth and to fall steadily while the spleen was attaining its maximum absolute weight. From 26 years on, the ratio fell slightly, except for an apparent rise from 50 to 65 years.

3. In general, male spleens were heavier than female spleens and those of white people heavier than those of blacks. As the difference between spleen weights of whites and blacks was greater than that between males and females, sex appears to be a less important factor than color. In none of the above categories were mean spleen weight differences of individual groups to be attributed to corresponding differences in mean body weights.

4. The average weight for all our adult spleens (16 years or over) was 150.7 gm.; for spleens between the ages of 16 and 70, 154 gm.; for all 4000 spleens, 140.7 gm.

5. The weight of the apparently normal human spleen fluctuates within extremely wide limits. Weights as low as 100 gm. and as high as 250 gm. were not infrequently recorded, while even such weights as 50 and 400 gm. were occasionally given for what appeared to be normal spleens.

6. Analysis of the cause of death in the "disease" group showed little beyond the prevalence of acute respiratory disease in the cases

between 16 and 25 years of age and of arteriosclerosis in the older age groups. The former of these may well be a factor in the spleen weight peak in the two young groups, and the latter a factor in the loss of spleen weight in older life. Analysis of the histologic appearances in the "disease" group showed that about 75% of the spleens had diagnoses of lesions which should tend to cause an increase in weight, and only 2.5% were listed as atrophic.

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THE SIGNIFICANCE OF PERIPHERAL CIRCULATORY DISTURBANCES FOR THE DEVELOPMENT OF OSTEO-ARTHRITIS.

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In 1909 Wollenberg¹⁸ elaborated the theory that vascular deficiencies are a primary factor in the production of osteo-arthritis. He based this theory on the frequent occurrence of arteriosclerosis of the vessels of the bone marrow and synovial membrane in osteo-arthritis (hypertrophic arthritis). Experimentally, he produced overgrowth of the patella in dogs by circular ligation of the soft tissues. Pemberton⁶ and his co-workers have repeated this experiment and supported Wollenberg's findings.

More recently Bernstein² pointed out that venous stasis may induce osteo-arthritis. After ligation of the popliteal veins in dogs he obtained degeneration of the articular cartilage of the knee joints, and after ligation of the lumbar vertebral veins he observed degeneration of the intervertebral disks, hypertrophy and osteophytes of the margins of the lumbar vertebrae.

On the other hand, the vascular theory was challenged by a number of authors. Pommer¹⁵ observed that arteriosclerotic changes in osteo-arthritic joints are not more frequent than in normal joints of individuals past middle age. Walkhoff,¹⁷ Axhausen and Pels¹ found that the changes of the patella after circular ligation are due either to minute injuries of the articular cartilage at the operation, or necrosis of the cartilage and bone, due to shutting off of the blood supply. The new bone formation is not due to osteophytes, as in osteo-arthritis, but to proliferation of fragments which are separated

from the patella by connective tissue. Axhausen advanced the theory that necrosis of articular cartilage induces the development of osteo-arthritis. Pommer regarded loss of elasticity of cartilage to be the initial lesion, which leads to reactive changes of the subchondral bone. Axhausen, Burkhardt,⁴ Seeliger,¹⁶ Haebler⁷ and Key⁹ produced osteo-arthritic changes in the joints of dogs, rabbits or guinea pigs by damaging the articular cartilage with physical and chemical means, such as cauterization or resection of small segments of articular cartilage or intra-articular injections of weak acid, alkali, or even normal saline solution.

TABLE 1.—RÉSUMÉ OF FINDINGS IN JOINTS OF LOWER EXTREMITIES AMPUTATED FOR GANGRENE DUE TO THROMBO-ANGIITIS OBLITERANS OR ARTERIOSCLEROSIS.

Case No.	Age.	Diagnosis.	Duration (yrs.)	Joints.	Remarks.
1	23	Thrombo-angiitis obliterans	4	Normal	Two amputations.
2	35	" "	10	Normal	
3	59	" "	10	Synovitis of ankle and knee joints. Inflammatory infiltration and thrombosis of synovial vessels. Erosions of the articular cartilages of the talus, tibia, femur and patella	Osteomyelitis second phalanx of large toe and tarsal bones.
4	64	Arteriosclerosis Mönckeberg type	..	Slight erosion of articular cartilage of femur and patella	
5	64	" "	2	Obliteration and thickening of vessels in synovial membrane. Tarsal and ankle joints normal. Moderate erosion of articular cartilage of femur	Two amputations. Osteomyelitis of second phalanx, large toe. Died.
6	74	" " "	8 mo.	Normal	Gas infection.
7	56	" " "	2	Synovial membrane normal. Normal vessels prevail. Some show thickening and obliteration. Moderate erosion and osteophyte of ankle and knee joints	Two amputations. Osteomyelitis and supuration of stump of large toe.
8	48	Arteriosclerosis with diabetes	12	Normal	Gangrene 6 wks. Osteomyelitis of large toe.
9	58	" " "	2	Erosion of cartilage of patella and femur. Hyperemia of infrapatellar fat pad	Two amputations.
10	59	" " "	12	Normal	Died.
11	59	" " "	7 mo.	Moderate hypertrophy of synovial membrane. Advanced osteoarthritis of knee joint	No history of joint complaint.
12	66	" " "	1	Synovial membrane normal. Slight erosion of patellar cartilage	Two amputations. Roentgen ray shows calcified vessels. Osteomyelitis of phalanx of large toe.
13	68	" " "	18	Normal synovial membrane. Erosion of articular cartilage of patella and femur	Two amputations.

The experimental evidence of these theories is subject to objections. Frequently, the methods employed were non-physiologic. Due to the small size of the joints of the animals, the action of the agent cannot be strictly localized. Finally, the changes may resemble, but are not identical with osteo-arthritis.

It occurred to me that the study of human joints in cases of severe, chronic organic diseases of peripheral blood-vessels would

give a more pertinent evaluation of the rôle of the vascular disturbances as a factor in the development of osteo-arthritis.

Material and Methods. The joints and blood-vessels of 13 lower extremities, which had been amputated because of gangrene due to arteriosclerosis or thrombo-angiitis obliterans, were studied

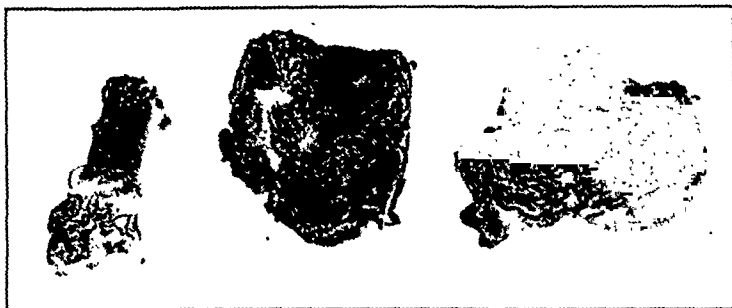


FIG. 1.—Thrombo-angiitis obliterans (Case 3). The metatarsus of the great toe, the articular surfaces of the tibia and talus show secondary osteomyelitis and supuration, which has spread from the gangrenous area.

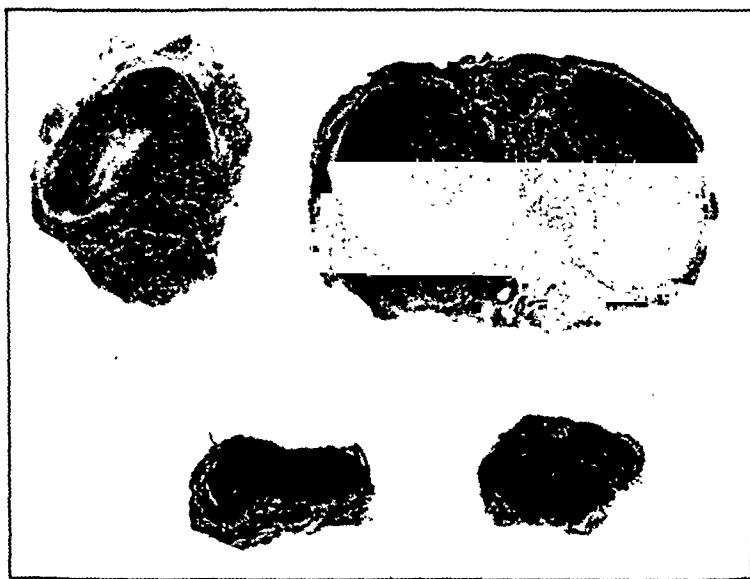


FIG. 2.—Thrombo-angiitis obliterans (Case 3). The articular surfaces of the first and second phalangeal joints of the large toe are intact. The patella and tibia show central erosions of the cartilage and thickening of the synovial membrane.

macroscopically and microscopically. Table 1 gives a summary of the findings. Thrombo-angiitis obliterans was present in 3 cases and arteriosclerosis was found in 10 cases. Of the latter group, 6 cases were complicated by diabetes mellitus. In 5 cases amputations had been performed at lower levels, such as toes or ankles, several months previously. Two cases (2 and 12) had bilateral amputations.

The patients who suffered from thrombo-angiitis obliterans were males between 23 and 59 years. In the arteriosclerotic group, there were 4 females and 6 males ranging in age between 48 and 74 years. The area of gangrene varied from the dorsum of one toe to extensive

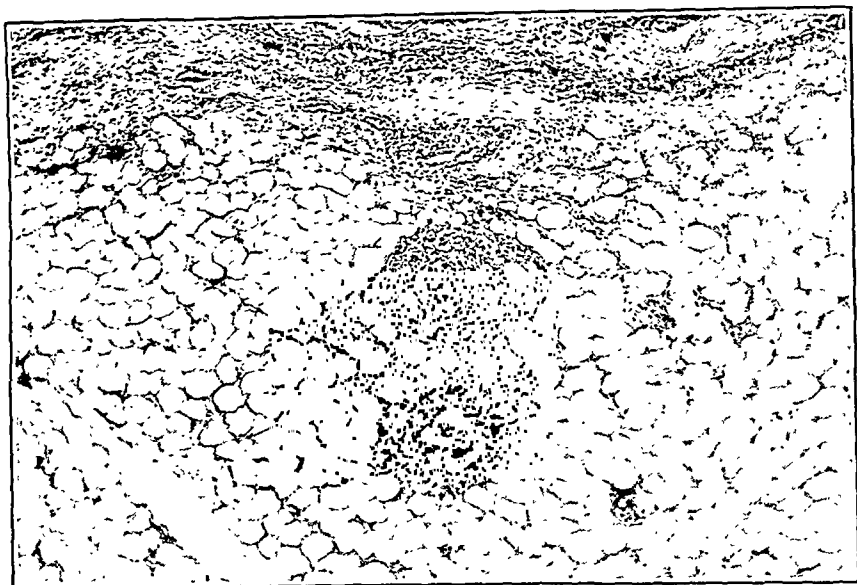


FIG. 3.—Thrombo-angiitis obliterans (Case 3). Section through the infrapatellar fat pad. Subacute synovitis with hypertrophy fibrosis and focal infiltration of the synovial membrane. Larger vessels are infiltrated and thickened but numerous newly formed small vessels are open. In the subsynovial fat, two large thrombosed and obliterated vessels are seen.

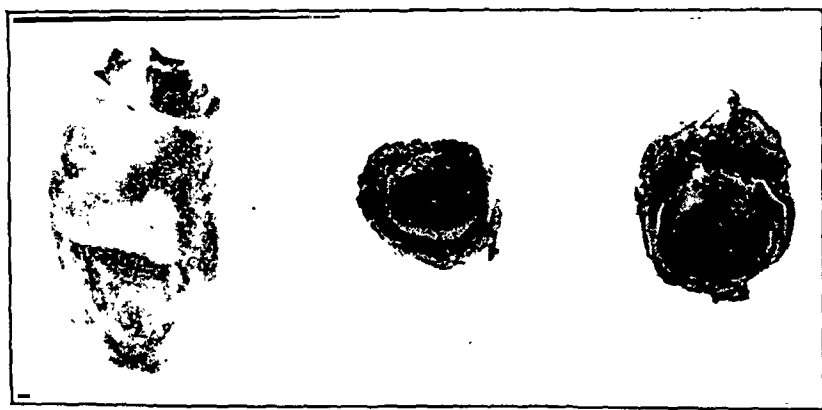


FIG. 4.—Thrombo-angiitis obliterans (Case 1). Gangrene of the left toe. The articular surfaces of the heads of the first and fifth metatarsals are intact. The surrounding joint capsules were normal.

necrosis of the foot and ankle. Osteomyelitis of the phalanges, tarsal bones or talus (Figs. 1, 7) was present in 4 cases. Only in 3 cases was the duration of clinical symptoms of circulatory disturbance less than 1 year. None of the patients gave a history of previous joint affections.

The Vessels of the Extremities. In all cases the femoral, tibial, peroneal, dorsalis pedis vessels and their small branches showed extensive and progressive lesions. In the cases of thrombo-angiitis

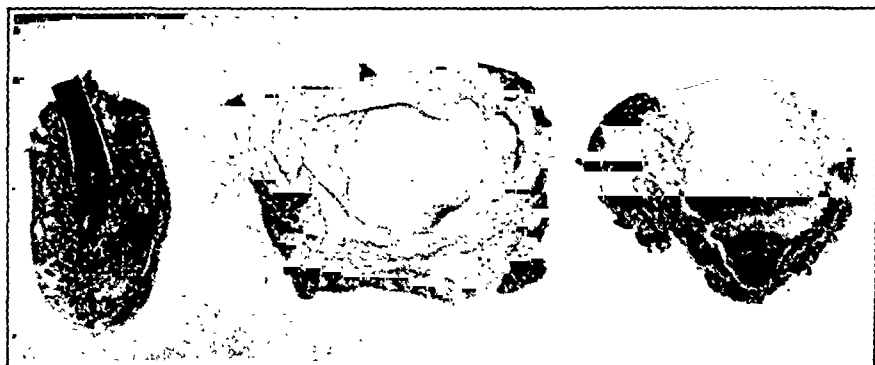


FIG. 5.—Thrombo-angiitis obliterans (Case 1). Section through the gangrenous toe. The plantar tendon intact. The articular surfaces of the talus and tibia and the synovial membrane are normal.

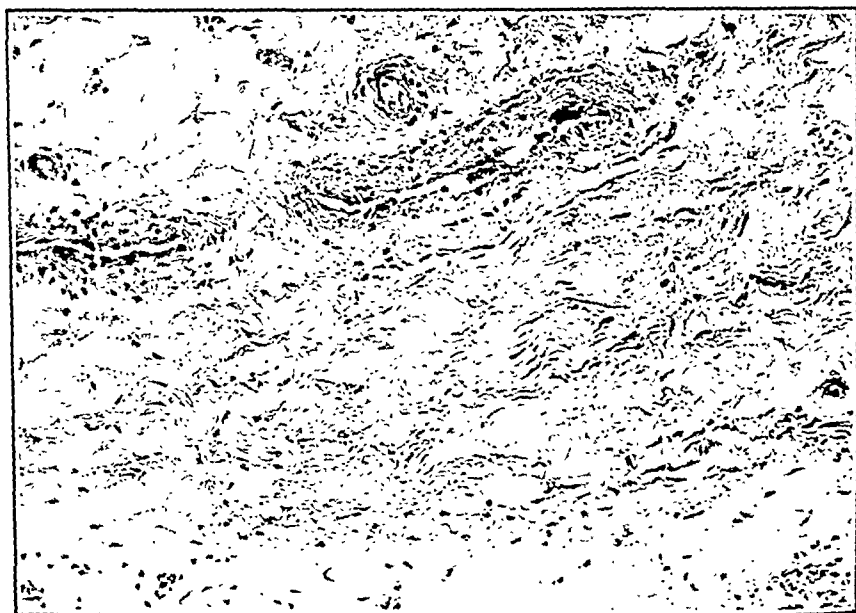


FIG. 6.—Thrombo-angiitis obliterans (Case 1). Normal synovial membrane of the lateral parts of capsule. Surface layer contains one to several rows of cells, sub-synovial layer, partly areolar, fatty or fibrous. Smaller vessels normal, larger vessels somewhat thickened.

obliterans, more recent infiltration of the vessels and thrombosis was found, together with various stages of occlusion by fibrotic organization. In cases of arteriosclerosis, the vessels were narrowed or obliterated by thickening of the intima and media through

atheromatous and calcareous masses, by secondary inflammation and thrombosis and fibrotic organization. The sclerotic vessels were in some cases visualized in roentgenograms.



FIG. 7.—Arteriosclerosis, Mönckeberg type, (Case 5). Osteomyelitis of the first phalanx of the large toe. The articular surfaces of the metacarpus, the talus and patella are normal.

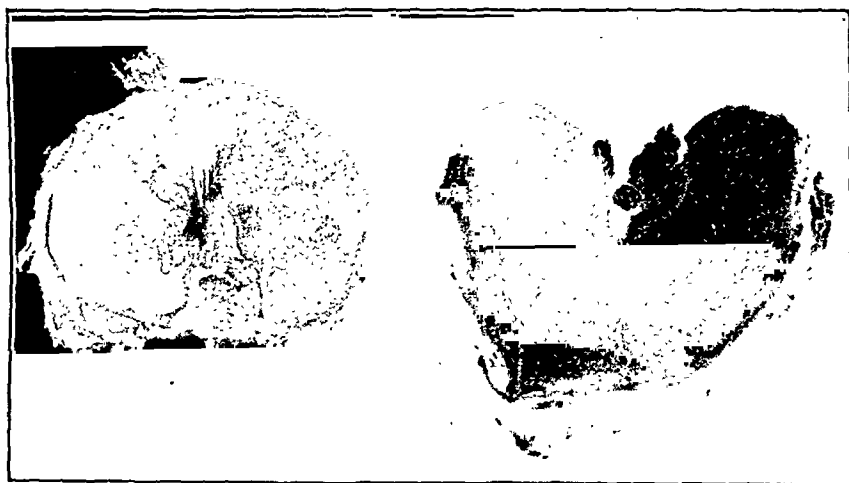


FIG. 8.—Arteriosclerosis, Mönckeberg type (Case 5). The articular cartilage of the knee joint shows fibrillation. In the central portion of the femur there is a deeper defect present.

The Synovial Membrane. In a case of thrombo-angiitis obliterans (Case 3), there was a subacute synovitis of the ankle and knee joints. The subsynovial tissue showed fibrosis and infiltration with round and plasma cells (Fig. 3). In 2 cases the synovial membrane was normal (Fig. 6). In 1 case of arteriosclerosis with advanced osteo-arthritis (Case 11), there was a moderate thickening of the

synovial membrane. In another case (Case 9), the infrapatellar fat pad was congested and showed hypertrophy. In 10 cases, the synovial membrane of the phalangeal, tarsal, ankle and knee joints appeared to be normal. In 4 cases, osteomyelitis spread, secondarily, to the phalangeal, tarsal and ankle joints.



FIG. 9.—Thrombo-angiitis obliterans (Case 3). Section through the articular surfaces of the tibia showing incipient osteo-arthritis. The hyaline cartilage shows fibrillation and erosion. Smaller and larger clefts are seen in horizontal as well as vertical direction. In the deeper layers of the cartilage enlarged lacunæ with numerous cartilage cells are present. The irregular dark blue line of calcified cartilage and the subchondral bone plate are broken through in a number of places by cellular bone marrow, which contains giant-cell osteoclasts. A small and a large fragment of fractured necrotic bone lamellæ are seen in the middle and the right lower corner. The bone marrow is hyperemic and contains numerous newly formed vessels.

Synovial Vessels. In 1 of the 3 cases of thrombo-angiitis obliterans (Case 3), numerous vessels showed either inflammation and thrombosis or obliterating fibrosis, but others were found patent. Newly formed vessels were also present in the inflammatory areas (Fig. 3). In the arteriosclerotic group, marked changes in the synovial vessels were found in 2 cases (Cases 5 and 7). In all cases some vessels showed thickening of the intima and media, and even obliteration. Such changes, however, are found in normal joints in people past middle age. In a group with such advanced arteriosclerosis, it is remarkable to note the slight degree of change in the synovial vessels.

The Articular Cartilages. One case (Case 11), a woman aged 64 years, showed advanced osteo-arthritis of the knee joint. The

central portion of the cartilages of the femur, tibia and patella were eroded. The underlying bone showed eburnation, and osteophytes at the periphery. The patient, however, denied having any previous symptoms in this knee. In another case (Case 7, Fig. 8) there was erosion of the central portion of the articular cartilage of the patella, tibia and femur. Fibrillation of the cartilage was found in 6 knee and in 4 ankle joints. In 5 extremities, the joints were entirely normal. Even in the cases with lesions in the knee and ankle joints, the majority of the phalangeal and tarsal joints were intact (Figs. 2, 4, 5, 7). Bone changes varied from simple atrophy and decalcification to osteomyelitis with massive destruction and suppuration of the phalanges and tarsal bones (Figs. 1, 7). In such places, marked periostitis was present.

Under the areas of fibrillation or erosion of articular cartilage, reactive bone changes occur. These consist, first, of localized absorption of the subchondral compact bone and the calcified zone of cartilage by the invasion of cellular bone marrow, which contains mononuclear and giant cell osteoclasts (Fig. 9). Subsequently, osteoid tissue is laid down by a seam of osteoblasts and finally impregnated with lime salts. The proliferation of the new bone, which replaces the destroyed cartilage, may produce osteophytes. The cellular and fibrotic marrow is hyperemic and contains numerous newly formed vessels. In the fatty marrow the vessels were sparse but mostly normal.

Periarticular Tissues. The joint capsule, ligaments and tendons were normal, except in the immediate vicinity of gangrenous areas. Even in such instances, the involvement of tendons were often minimal (Fig. 5).

Discussion. From this study the following conclusions can be drawn:

1. In cases of advanced thrombo-angiitis obliterans, the synovial vessels may participate to a marked degree in the generalized inflammatory vascular lesions.

2. In severe arteriosclerosis with gangrene, the synovial vessels have been found only slightly or moderately involved. Various factors may contribute to the resistance of the synovial vessels against arteriosclerotic changes. First, the synovial membrane is supplied by a rich vascular network. The numerous anastomoses reduce the circulatory burden on any single blood-vessel. Secondly, Oberndorf¹⁴ pointed out that the localization of arteriosclerosis is influenced by the amplitude of excursion of a blood-vessel, which is permitted by the surrounding tissue. Blood-vessels, which are located in osseous channels, such as the internal carotid artery, or are firmly bound to the surrounding tissues, such as the iliac, femoral, tibial and dorsalis pedis arteries, show the most advanced arteriosclerosis. The synovial vessels participate in the joint motions. This exerts a massaging effect which opposes the progress of

arteriosclerotic lesions. Venous congestion was not found in these synovial membranes, except in 1 case where the infra-patellar fat pad was hypertrophied and congested. These findings contradict the theory that vascular changes, especially arteriosclerosis, are a primary factor in the etiology of arthritis.

Lesions of the articular surfaces were not any more frequent than those found in a corresponding age group with normal extremities. All 10 patients with arteriosclerotic gangrene were over 40 years of age, only 2 (20%) of the cases showed a fully developed picture of osteo-arthritis. Numerous investigators have found some degeneration of articular cartilage and osteophytes in over 80% of people past middle age. Besides the slight degree of arteriosclerosis in the synovial vessels, other evidence confirms that these degenerative changes are not due primarily to vascular deficiency. The knee and ankle joints were usually more involved than the phalangeal and tarsal joints, while the greatest deficiency of circulation occurs in the distal part of the extremities. Secondly, the articular cartilage has an extremely low metabolic rate and very slight nutritional requirements (Bywaters).⁵ Therefore, it is apt to be not greatly affected by deficiency of circulation. Finally, the initial lesions of osteo-arthritis consisting of fibrillation and erosion occur in the central portion of articular cartilage which is devoid of blood-vessels. While all the factors which induce this degeneration of articular cartilage are not known, wear and tear by prolonged use, mechanical stresses, overweight and trauma undoubtedly play an important rôle.

Individual variations of onset and progress of these changes are partly explained by constitutional factors. Structural inferiority of the cartilage and malformation of the joint surfaces predispose to early development of osteo-arthritis. The endocrine system, especially the hypophysis, has a powerful influence on the metabolism and growth of bone and cartilage. Imbalance of this system will induce pathologic changes. This is evidenced by the arthropathy in juveniles who suffer from lesions of the pituitary gland and by the osteo-arthritis which is associated with acromegaly. Middle and advanced ages are characterized by involution of the gonads and hypertrophy of the pituitary gland. This offers some explanation of the prevalence of osteo-arthritis among women at the menopause.

In contrast to the articular cartilage, the metabolism, blood supply and nutritional requirement of the bone are high. Consequently, bone is greatly affected by vascular lesions. Decalcification, atrophy, and even necrosis and absorption of phalanges were sometimes found in arteriosclerosis and thrombo-angiitis obliterans.

In Raynaud's disease and scleroderma, interference with the blood supply leads to a characteristic absorption of the terminal phalanges (Buerger³). Venous congestion in chronic heart and lung

diseases may produce hypertrophy (clubbing) of the distal phalanges, either alone or in association with toxemia (Locke¹²).

Clinical Consideration. The clinical symptomatology of osteo-arthritis confirms the conclusion that vascular changes play only a secondary rôle. The incidence of arteriosclerosis and hypertension is not much higher in patients with osteo-arthritis than in a corresponding group of the same age and sex. Kovacs *et al.*,¹¹ Kersley⁸ and Kling¹⁰ found that changes in the skin capillaries and skin temperature are not pronounced and not constant enough to be considered as a primary factor in the development of osteo-arthritis. The rôle of venous congestion and stasis seems to be negligible. McMasters¹³ found, out of 30 cases of varicose veins with long-standing passive congestion and edema, 21 cases did not show Roentgen ray evidence of osteo-arthritis of the ankle and feet. The remaining 9 cases which showed osteo-arthritic changes had chronic ulcers of the leg. In my own material, the incidence of osteo-arthritis was not higher in patients with varicose veins as compared with patients of the same age and sex with normal veins. The results of these investigations are important for an evaluation of the efficiency for our methods of treatment of osteo-arthritis.

The most commonly used chemical, physical or electrical applications aim to increase the circulation in the joints. Recently, even surgical procedures, like drilling through the head of the femur, were recommended with this purpose in mind. The limited rôle of vascular disturbance in the pathogenesis of osteo-arthritis makes it evident that such procedures can only have a transitory symptomatic and alleviating effect, but are not sufficient to combat the underlying cause of the disease.

On the other hand, the importance of protection of the articular cartilage against excessive wear and tear is not sufficiently appreciated. Rest, correction of mechanical unbalance, and the reduction of abnormal pressure and weight-bearing offer more direct measures for prevention and checking of degenerative articular changes. As a last resort in advanced osteo-arthritis, surgical procedures, such as shelf or bifurcation operations, are justified in order completely to abolish motion or to diminish weight-bearing.

Summary. 1. The joints and blood-vessels of the lower extremities, amputated for gangrene, in 3 cases of thrombo-angiitis obliterans and in 10 cases of arteriosclerosis were studied.

2. In both groups the vessels of the extremity showed advanced lesions. The synovial vessels were normal or only moderately affected in the cases of arteriosclerosis. In thrombo-angiitis obliterans the synovial vessels were found to be more frequently involved. The synovial membrane was normal, except for localized hypertrophy in 2 cases of the arteriosclerotic group. One case of thrombo-angiitis obliterans showed subacute synovitis of ankle and knee joints. Venous congestion of the synovial membrane was found in 1 case.

3. Pronounced osteo-arthritis was present in only 2 cases. Slight erosions of the articular cartilage were found in all cases past 40 years. The incidence and extent of these changes correspond to that usually found in a similar age group with normal blood-vessels. On the basis of these findings the vascular theory of osteo-arthritis is contradicted.

4. On the other hand, articular cartilage is damaged by wear and tear of use, and by abnormal pressure, and weight-bearing. Age, mechanical and traumatic factors, therefore, play an important rôle in the development of osteo-arthritis. Constitutional inferiority of bone and cartilage or malformations of the bearing surfaces are apt to hasten and accentuate the development of osteo-arthritis. Cartilage and bone growth are profoundly influenced especially by the hypophysis. Imbalance and dysfunction of the endocrine system in advanced age and especially at the menopause explain the onset of osteo-arthritis and the prevalence in women past 40.

5. Bone has a higher metabolic rate and nutritional requirements, and is therefore susceptible to vascular disturbances. Atrophy, decalcification and, in extreme cases, also necrosis and absorption occur in arteriosclerosis, thrombo-angiitis obliterans, Raynaud's disease and scleroderma. Bone hypertrophy of the end phalanges, due to venous congestion, is quite common in chronic heart and lung diseases.

6. Clinical evidence also shows that vascular disturbance is only a secondary factor in osteo-arthritis. Organic or functional changes of the blood-vessels, blood pressure, and flow, and changes in the skin capillaries are not much more frequently found and are not more pronounced than in patients of a corresponding age group which do not suffer from osteo-arthritis.

7. Therapeutic measures to augment the circulation in osteo-arthritis are not directed against the primary cause; therefore the effect is mostly transitory and only symptomatic.

8. Protection of the joint by rest, correction of abnormal pressure, weight-bearing and, as a last resort, operative procedures which eliminate or decrease motion, offer a more efficient way of prevention and arresting of the degeneration of articular cartilages.

9. Imbalance and dysfunction of the endocrine system and especially a preponderance of the hypophysis at the menopause is a factor in the development of osteo-arthritis. It is hoped that advance in endocrine therapy will open new possibilities of combating osteo-arthritis.

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SPECIFIC TREATMENT OF PNEUMOCOCCUS TYPE II PNEUMONIA.

INCLUDING THE USE OF HORSE AND RABBIT ANTIPNEUMOCOCCUS
SERUMS AND SULPHANILAMIDE.

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Most workers with extensive experience have succeeded in demonstrating quite regularly a striking reduction in death rate with specific serum therapy in cases of pneumococcus Type I pneumonia. The results in cases due to the Type II pneumococcus have varied with different observers, most of whom could demonstrate only slight reductions in mortality.^{1a, b, 2, 5a, b, 12, 13} Widely divergent results have been reported in different years from the same clinic. Thus, at Bellevue Hospital almost no appreciable effect on the death rate was noted over a period of 5 years, but in the sixth year there were only 3 deaths among 21 treated cases (14.3%) as compared with 13 deaths among 20 controls (65%). During that year only patients admitted to the hospital within 72 hours of the onset were included in the study and every alternate case was given specific serum.² At the Boston City Hospital, the mortality in the cases treated with serum was 23% during 1929-32 as compared with 42% during the following 3-year period. This difference was ascribed to the marked discrepancy in the dosage employed in these 2 periods, the average dose of antibody per patient being 3 times as great in 1929-32 as in the following 3 years.^{5a} A considerably larger number of cases of pneumococcus Type II pneumonia have been treated with specific antibody at the Boston City Hospital

since the time of the last report. It is of interest to present the results of therapy in these cases which include a small number treated with rabbit antipneumococcus serums and others treated with a combination of specific serum and sulphanilamide.

Patients, Materials and Methods. In general, the choice of patients for treatment with serum, the methods of pneumococcus typing and of serum administration, the selection of cases for supplementary treatment with sulphanilamide, and the manner in which this drug was used were all essentially the same as those employed in the Type I cases and are described in the previous paper.⁴ Only the features pertaining to the Type II cases will be noted.

Attention has previously been called to the close association of the Type II pneumococcus with primary lobar pneumonia in adults.^{5b,6} This has been fully corroborated by the more recent experience. Among 500 patients from whom this organism was obtained during the past 9 years at the Boston City Hospital, 452 (90.4%) were adults with pneumonia. In only 17, or less than 4% of the latter, was the pulmonary lesion atypical (bronchopneumonia) and almost all of these were cases first diagnosed at autopsy and were secondary to other serious disease. On the other hand, only 4% of the cases of Type II pneumococcus lobar pneumonia were "secondary." In only 10 instances (2%) was this type obtained from sputum or from pharyngeal cultures of persons without acute pneumonia. All the remaining cases were either admitted with empyema (4%) or the organism was obtained from a focal suppurating lesion (3.6%).

Reliability of Neufeld Typing. In the past 3 years a diagnosis of Type II pneumococcus made directly from the sputum by the Neufeld method proved to be wrong in only 1 instance (both the heart's blood of the mouse inoculated with the same sputum and the patient's blood culture proved to be Type I); and 4 sputa containing Type II pneumococci were incorrectly typed by this method, the proper type being discovered by mouse inoculation of the same specimen and by direct examination of subsequent specimens. (These were originally called Types I, V, VII and VIII, respectively, and given serum for these types until the correct type was determined.) In 6% of sputa from cases of Type II pneumonia, the direct examination by the Neufeld method failed and the type was obtained from the same specimens after mouse inoculation.

Serums. A total of 70 lots of concentrated Type II antisera were used during this 3-year period. These included 64 horse serum lots varying in potency from 1000 to 3000 units of Type II antibody per cc., as compared with the National Institute of Health standard serum P11, to which a value of 150 Type II units per cc. has been assigned. Of these, 21 contained less than 1500, 26 had between 1500 and 2000, and 17 had more than 2000 units per cc. Only 9 of these were monovalent, the rest contained Type I antibodies in the same or up to 3 times the concentration of Type II units. The 6 lots of concentrated rabbit serum used ranged in potency from 4000 to 9000 units per cc.

Dosage. The total initial dose for young adults with sterile blood cultures treated before the end of the fourth day of the disease was usually 80,000 to 100,000 units. This was given in the same manner as the Type I serums, except that somewhat larger volumes were frequently given for the second or subsequent injections. Larger doses were given under the conditions previously noted for Type I cases.⁴

Results. Gross Mortality. The death rates during the last 3 years among the serum treated and non-serum treated cases are shown in Table 1. The figures for the 2 previous 3-year periods are included

for comparison, and the percentage of serum recipients among all cases in which the diagnosis of pneumococcus Type II pneumonia was made during life are also given. While the death rates have varied widely during each of the past 3 years among both the

TABLE 1.—MORTALITY AMONG CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA AT THE BOSTON CITY HOSPITAL.

Years.	Serum treated.			Non-serum treated.			Serum treated, %
	No.	Died.	Died, %	No.	Died.	Died, %	
1929-32	48	11	23	89	40	45	35
1932-35	38	16	42	43	20	46	47
1935-36	43	5	12	33	8	24	57
1936-37	52	15	29	19	8	42	73
1937-38	53	8	15	12	7	58	82
1935-38	148	28	19	64	23	36	70
1929-38	234	55	24	196	83	42	54

In this and in subsequent tabulations of death rates, none of the cases treated with serum are excluded. Those non-serum treated fatal cases in whom the Type II pneumococcus was first identified from autopsy material were excluded. There were 8 such cases in each of the 2 earlier 3-year periods and 3, 1 and 2 cases, respectively, in the 3 succeeding years.

serum treated and the non-serum treated cases, they have remained consistently and significantly lower among those treated with serum. This has been true in spite of the steady increase in the proportion of cases so treated. It is to be borne in mind, however, that the

TABLE 2.—INCIDENCE OF BACTEREMIA AND ITS RELATION TO THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL).

Years.	Serum treated.							Non-serum treated.						
	Bacteremic cases.			%	Non-bacteremic cases.*			Bacteremic cases.			%	Non-bacteremic cases.*		
	No.	Died.	Died, %.		No.	Died.	Died, %.	No.	Died.	Died, %.		No.	Died.	Died, %.
1929-35 ³	29	18	63	34	57 ¹	9	16	53	38	72	40	79 ¹⁰	22 ¹²	28
1935-36	13	3	23	30	30 ¹	2 ¹	7	9	6	67	27	24 ¹	2	8
1936-37	20	10	50	38	32	5	16	7	7	100	37	12 ¹	1 ¹	8
1937-38:														
Horse	20	7	35	45	24	1	4	5	5	100	42	7	2	29
Rabbit	4	0	0	44	5	0	0							
1935-38	57	20	35	39	91	8	9	21	18	86	39	43 ⁵	5 ¹	29
1929-38	86	38	44	37	148 ²	17 ¹	12	74	56	76	39	122 ¹⁵	27 ¹³	22 ²⁹

* Include cases in which no blood cultures were made. The numbers are shown by superscripts.

non-serum treated cases are not really controls, as already noted in the previous paper.⁴ Some of the more significant factors concerned in the death rates will be considered in order to shed some light on the differences observed.

Bacteremia. The incidence of bacteremia and its effect on the death rates are shown for the different years in Table 2. It will be seen that the low death rate among both the serum treated and non-serum treated cases in 1935-36 was associated with a relatively low incidence of bacteremia in each instance. During the following year, the higher death rate among the serum treated cases accompanied the inclusion of a large proportion of cases in which serum treatment was begun late in the disease (see Table 5). In the last year, a small number of cases were treated with rabbit serums. There were no deaths among these cases. However, the death rate among the cases treated with horse serums during the same year was also low.

TABLE 3.—RESULTS OF MULTIPLE BLOOD CULTURES IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA. (BOSTON CITY HOSPITAL, 1935-38).

	Number of cases.	
	Recovered.	Died.
<i>Multiple blood cultures before the first dose of serum (50 cases).</i>		
All positive	8	6
First negative, later positive	7	1
All negative	24	4
First positive, later negative	0	0
<i>Results of multiple blood culture in relation to treatment in 17 fatal cases.</i>		
Positive before and after serum		8*
Positive before serum and negative later		2
Negative before and after serum		3
Negative before serum and positive later		4
<i>Multiple blood cultures during the acute disease in non-serum treated cases.</i>		
All negative	7	0
First negative, then positive	1	1
First positive, then negative (fatal cases)		3
Two or more positive	0	8

* In 2 of these cases the blood cultures were negative for several days after treatment was begun and later ones were again positive.

During 1929-32, a number of cases not treated with serum developed bacteremia while under observation, but no cases were encountered in which positive blood cultures were first obtained after serum treatment was begun.⁶ Two such cases were subsequently noted.⁵ The significant results in the cases in which multiple blood cultures were done during the past 3 years are shown in Table 3. The 14 cases whose earlier cultures were negative and who later had positive cultures are of special interest. The bacteremia first appeared before serum was given in 8 of these cases and after serum treatment in 4. One of the former and all the latter died. The other 2 cases received no serum and 1 died. Among the bacteremic non-serum treated cases, 3 died in spite of the fact that later cultures of the blood were sterile.

Age. The distribution of cases by decades is shown in Table 4. A large number of cases treated with serum were in the older age

groups. There were relatively more cases in the older age groups among the non-serum treated cases, but a greater proportion of the younger serum treated cases had positive blood cultures. The usual increase in mortality and in the incidence of bacteremia with

TABLE 4.—INFLUENCE OF AGE ON DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL, 1935-38).

Age group, yrs.	Serum treated.*							Non-serum treated.						
	Bacter-emic.		Non-bac-teremic.†		All cases.			Bacter-emic.		Non-bac-teremic.†		All cases.		
	No.	Died.	No.	Died.	No.	Died.	Died, %.	No.	Died.	No.	Died.	No.	Died.	Died, %.
12-19 . . .	7 ¹	0	18 ²	0	25 ³	0	0	0	..	11	0	11	0	0
20-29 . . .	4	1	17	0	21	1	5	1	1	2	1	3	2	67
30-39 . . .	14 ²	1	22 ²	1	36 ⁴	2	6	2	1	11	1	13	2	15
40-49 . . .	15	8	18 ¹	2	33 ¹	10	30	5	4	12	2	17	6	35
50-59 . . .	7	4	6	2	13	6	46	7	6	4	1	11	7	64
60-69 . . .	10 ¹	6	8	3	18 ¹	9	50	4	4	3	0	7	4	57
70+ . . .	0	..	2	0	2	0	0	2	2	0	..	2	2	100
Total . . .	57 ⁴	20	91 ⁵	8	148 ⁹	28	19	21	18	43	5	64	23	36

* Includes cases treated with rabbit serum; the numbers are indicated by superscripts.

† Includes cases in which blood cultures were not done. (See Table 2.)

TABLE 5.—INFLUENCE OF THE DURATION OF THE DISEASE WHEN SERUM TREATMENT WAS BEGUN ON THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA.

		Day treatment begun.								
		Fourth day or before.			Fifth day.			Sixth day or later.		
		No.*	Died.	Died, %.	No.*	Died.	Died, %.	No.	Died.	Died, %.
Bacteremic cases . .	1929-35	18	10	56	5	3	60	5	5	100
	1935-36	12	3	25	1	0	0	0		
	1936-37	12	3	25	2	1	50	6	6	100
	1937-38	17 ⁴	5	29	3 ¹	1	33	4	1	25
	1935-38	41	11	27	6	2	33	11	7	64
	1929-38	59	21	36	11	5	45	16	12	75
Non-bacter-emic cases	1929-35	36	5	14	12	1	8	10	3	30
	1935-36	30	2 [†]	7	0	0		
	1936-37	28	4	14	3	1	33	1	0	0
	1937-38	22 ⁴	0	0	2	0	0	5	1	20
	1935-38	80	6	8	5	1	20	6	1	17
	1929-38	116	11	10	17	2	12	16	4	25
All cases . .	1929-35	54	15	28	17	4	24	15	8	53
	1935-36	42	5	12	1	0	0	0		
	1936-37	40	7	18	5	2	40	7	6	86
	1937-38	39 ⁵	5	13	5 ¹	1	20	9	2	22
	1935-38	121	17	14	11	3	27	17	8	47
	1929-38	175	32	18	28	7	25	32	16	50

* The superscripts represent the numbers of cases treated with rabbit serums.

† Includes 1 case in which blood culture was not done.

advancing age is apparent among both the serum treated and non-serum treated cases.¹⁵ The death rates are generally lower among the serum treated cases in all age groups. The age distribution of the cases treated with rabbit serums was generally favorable.

Influence of the Time of Beginning Treatment. This is shown in Table 5. The greatest increase in death rate occurred when treatment was begun after the fifth day. The results of serum treatment begun after the fourth day were more favorable during the last year than in previous years. Treatment in the rabbit serum recipients was begun before the fifth day in all but 1 of the cases.

TABLE 6.—ANALYSIS OF THE AVERAGE DOSES OF SPECIFIC ANTIBODY USED IN THE TREATMENT OF CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL, 1935-38).*

	1935-36.	1936-37.	All cases.	1937-38. Horse serums.	Rabbit serums.
Volume per patient (cc.)	72	121	105	116	49
Units† per patient (thousands)	125	215	189	171	277
Units per cc. of serum	1740	1880	1800	1480	5650
Number of injections	4.0	6.3	5.5	5.7	3.8
Initial injection‡	8	8	8	8	6
Subsequent injections	39	40	40	35	98
Outcome:					
Recovered	150	209	186	154	277
Died	125	231	237	237	
Blood culture before treatment:					
Negative	114	109	166	153	236
Positive	150	305	216	194	328
Treatment begun:					
Fourth day or before	125	224	191	131	301
Fifth day	120	208	212	245	80§
After fifth day		171	166	166	
Age groups: 12-29 years	103	138	119	118	120
30-49 years	134	252	202	171	320
50+ years	156	206	250	228	540§
Average age (years)	35.1	39.4	38.5	39.6	32.7

* During 1929-32, the average amounts used were 169 cc. containing 453,000 units or 2680 units per cc.; during 1932-35 the average dose was 145 cc. containing 136,000 units or 940 units per cc.¹⁶

† The actual titrated units as standardized against the National Institute of Health standard serum P11 to which a value of 150 units of Type II antibody per cc. has been assigned. The values given on the labels were usually from 10 to 25% lower than these actual values.

‡ The figures from here down, except those in the lowest line, all represent thousands of units.

§ One case only.

Dosage. The average doses of Type II antibody used during the past 3 years are analyzed in Table 6. The average concentration of antibody in the serums used during this period was intermediate between that of the specially prepared and highly potent preparations available during 1929-32 and those of rather low potency used during 1932-35.¹⁶ Bacteremic patients received larger doses than non-bacteremic patients. While it was our purpose, in general, to give more antibody to patients in the older age groups and to those in whom treatment was delayed, a number of such patients were in such poor condition that the contemplated dose could not

be completed. In a few patients requiring large amounts of antibody, the treatment had to be discontinued because the available supply was exhausted. The rabbit serums had 4 times the concentration of antibody contained in the horse serums. Patients treated with the former received considerably larger amounts of antibody than those treated with horse serum, and these larger amounts were contained in a much smaller volume.

Clinical Response. The effect of serum treatment on the course of the disease was as striking during the past 3 years as was previously observed during the 1929-32 period.⁶ During 1935-38, 98 (86%) of the 114 serum treated patients who recovered without purulent complications were free of fever (oral temperature 100° F. or higher) and other symptoms of the acute disease within 48 hours after the first injection of serum, and 71 (62%) had a characteristic crisis within 24 hours of beginning treatment. During the same period only 12 (29%) of the non-serum treated cases who recovered had a similar change in the clinical condition within 48 hours of admission to the hospital and 50% were febrile and acutely ill 4 or more days in the hospital.

Among the 28 fatal serum treated cases, 6 died within 24 hours after the first dose of serum was given and 17 died more than 48 hours later. Of the 23 non-serum treated deaths, 7 occurred within 24 hours of admission and 14 occurred on the third day in the hospital or later.

Untoward Reactions. Both the immediate and the delayed reactions were somewhat more frequent and more severe than those encountered in the Type I cases during the same period.⁴ This may have been due to the fact that more injections were given to each patient and a greater volume was introduced with each of the individual injections, except for the initial ones (see Table 6). The incidence of the various reactions observed is summarized in Table 7.

Immediate reactions occurring during the injection or within a few minutes were observed in 42 patients treated with horse serum. Nausea and/or vomiting was the most frequent and usually accompanied by injection of lots of serum which gave chills frequently on the same or in other patients. In 2 of these cases the skin test with normal horse serum was positive and in a third the vomiting accompanied a skin eruption. In 5 instances the nausea and vomiting accompanied the first dose, but in the others it occurred only with later injections. Urticaria occurred with the initial injection in only 2 cases; in the others, it accompanied later ones. It first appeared in some cases after the fifth or sixth injection. In 4 instances it recurred after 2 or more injections. Among the patients with urticaria or asthmatic reactions, 4 had positive skin reactions, 3 had a recent history of serum injection (including one with a positive skin test) and 3 gave a previous history of asthma. Two patients complained of severe joint pains during each injection which subsided immediately after it was completed. Of the 23 patients who had immediate reactions, other than nausea and vomiting, 11 had serum sickness later. Circulatory collapse with pulmonary edema occurred during or shortly after the injection of horse serum in 2 instances and of rabbit serum in 1. One of the former was in poor general condition at the time and died after a few hours; the

others responded readily to stimulants. No other immediate reactions were observed with the rabbit serums.

Thermal Reactions. The frequency of these reactions varied from year to year. They were more common and more severe after the serums supplied by the State than after the Lederle serums that were available for clinical trial. They most frequently followed only 1 of the injections, which was usually one of the larger doses. Two of these reactions were severe and were followed by high fever (107° F.) but responded readily to treatment. There were 4 instances in which several injections of one lot of serum were given without untoward reactions and a chill occurred after the first injection of another lot of serum. In 3 patients treated with horse serums and in 1 treated with rabbit serum, the chill followed the initial intravenous injection after a larger amount had previously been given intramuscularly without febrile reaction. Aspirin (10 to 20 grains) was given before the injections in a number of instances during the last year. One or more chills occurred in 6 patients in spite of this drug.

TABLE 7.—UNTOWARD REACTIONS FROM THE USE OF SPECIFIC SERUM IN THE TREATMENT OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL, 1935-38).

	Horse serums (139 cases).	Rabbit serums (9 cases).
<i>Immediate reactions</i>	40 (29%)	1
Nausea and/or vomiting	17	0
Marked dyspnea or asthma	6	0
"Collapse" with pulmonary edema	2	1
Urticaria	13	0
Joint pains	2	0
<i>Thermal reactions</i>	60 (43%)	5
One chill	44	2
Two chills	11	3
Three chills	5	0
After initial intravenous injection only	11	1
After first and other injections	6	3
Only after second and/or later injections	43	1
Lederle lots on clinical trial (horse, 66 cases; rabbit, 9 cases)		5
1935-36 (12 cases)	14 (21%)	
1936-37 (24 cases)	6 (50%)	
1937-38 (horse, 30 cases; rabbit, 9 cases)	5 (21%)	
State serums* (84 cases†)	3 (10%)	5
1935-36 (32 cases)	48 (57%)	
1936-37 (34 cases)	20 (63%)	
1937-38 (18 cases)	15 (44%)	
1937-38 (18 cases)	13 (72%)	
<i>Delayed serum sickness</i>	44 (32%)	5
Fever only	5	2
Rash	5†	0
Arthralgia	17‡	2
Arthralgia and rash	17‡	1

* Including some lots on clinical trial.

† 11 cases received both state and commercial lots; 2 had chills from both.

‡ Superscripts represent cases with enlarged lymph nodes.

Serum Sickness. Arthralgia, with or without urticaria, was the most frequent symptom. Fever occurred in almost every case; in 2 of the severe cases it reached 104° F. In 1 patient the symptoms were ushered in with a chill. The duration of the serum sickness was usually 1 to 3 days, although in some cases symptoms lasted as long as 10 days. The symptoms were considered severe in 5 of the horse serum recipients and in 1 of those treated with rabbit serum. The latter had edema of the face in addition to the rash and arthralgia.

Complications Among Recovered Cases. Among the serum treated cases, 4 developed empyema requiring surgical drainage. One of these patients received rabbit serum. In 4 other patients, all of whom were treated with horse serums, pneumococci were demonstrated only in the pleural fluid at the first thoracentesis but later fluids showed no organisms on smear or culture. In 1 of the latter cases the earlier organisms were demonstrated by culture and in the other 3 they were seen only directly in the fluid but cultures of the same fluid yielded no growth. One of the latter had a sterile blood culture and the other 7 cases had positive blood cultures before serum treatment was begun. Large sterile effusions (250 cc. or more) were demonstrated by thoracentesis and culture in 4 additional patients, including 1 bacteremic rabbit serum recipient and 3 non-bacteremic patients treated with horse serum. Purulent otitis media developed in 2 cases, but only 1 of these yielded Type II pneumococci on culture. One of the empyema patients also had an abscess of the leg and purulent arthritis from which the specific organisms were cultured and which required surgical drainage. Thrombophlebitis occurred in 2 of the rabbit serum recipients. Two pregnant women, including 1 with empyema, had a miscarriage during the acute disease.

Among the non-serum treated patients who recovered, 1 had empyema requiring operation, 1 had otitis media and a third had septic parotitis. Type II pneumococci were cultured from the pleural and aural exudates but not from the parotid pus. The septic complications in the fatal cases will be considered below.

Fatal Cases. A review of the fatal cases of pneumococcus Type II pneumonia indicates that, for the most part, death was associated with the severity of the pneumonia or its complications. In the cases treated with serum, the poor general condition of the patients when treatment was begun was a major factor in many instances. No doubt the fact that the reactions were frequent with the serums available during this period militated against the use of adequate dosage and counteracted appreciably the beneficial effects of the antibody.

Among the serum treated patients 8 had evidence of peripheral vascular collapse (stupor, low blood pressure, cold clammy skin and ashen gray color) and/or beginning pulmonary edema at the time treatment was begun, and 2 of these patients had auricular fibrillation in addition. Death occurred within a few hours in 4 of these cases and in the others the condition precluded adequate serum treatment. A similar condition developed after treatment was begun in another patient with auricular fibrillation treated on the sixth day and in 1 pregnant patient. The latter had chills after each of 3 injections, delivered a stillborn baby during the third of these chills and died shortly thereafter. Meningitis was demonstrated soon after treatment was begun in 2 patients, 1 of whom proved to have endocarditis, in addition, at autopsy. In 2 other bacteremic patients, empyema was present when treatment was begun. In 1 of these, bacteremia persisted for several days and endocarditis was probably present (there was no autopsy). Alcoholism was probably directly responsible for the death in

2 cases; 1 was in coma when treatment was begun and died in 6 hours, and the other survived for several days and died in delirium tremens during extreme uncontrolled activity. There was 1 patient who was admitted for alcoholism, a fractured skull and probably fractured ribs. His pneumonia improved following treatment but he died suddenly with acute dyspnea 16 days later. In another patient, autopsy revealed a large aortic aneurysm compressing one entire lung. In the 10 remaining patients either the dosage was inadequate or there was too long a delay between injections or else the serum was ineffective. Bacteremia first developed 4 or more days after treatment was begun in 3 of these patients.

Among the fatal non-serum treated cases, 3 had empyema and 1 of these developed meningitis 3 weeks after surgical drainage. Purulent complications were present in 2 other patients; meningitis in 1 and arthritis in the other. In 1 patient the symptoms suggested perforated peptic ulcer but neither operation nor autopsy was performed. The other patients all died of uncomplicated pneumonia.

Résumé of Cases Treated With Rabbit Serum. (See Tables 2, 4, 5, 6 and 7.) Nine cases of pneumococcus Type II pneumonia were treated with rabbit serums and all recovered. The average dose was larger in terms of units but smaller in volume compared with that used in the horse serum treated cases. Four of the patients had positive blood cultures, including a woman of 67 in whom treatment was begun at the end of the fourth day and was supplemented with sulphanilamide. One other non-bacteremic patient was 43 years old, and the remaining patients were under 40. One of the bacteremic patients who received 300,000 units on the first 2 days of the disease developed empyema which required surgical drainage. Immediate reactions of the "allergic" type (urticaria and asthma) did not occur, but 1 patient developed low blood pressure, rapid pulse and slight pulmonary edema after the second and third injections but responded readily to stimulants in each instance. Chills and serum sickness were about as frequent as among the horse serum recipients.

Cases Treated With Sulphanilamide. The use of this drug in pneumococcus Type II pneumonia was reserved, in general, for the severest cases, particularly when they were seen late in the disease. Only 1 such patient was treated with the drug alone and that patient died before any appreciable amount could be given. The relevant data in 8 patients treated during 1937-38 with the combination of specific serum and sulphanilamide are shown in Table 8.

The average age of these 8 patients was 59 years. The only patient in this group who was under 50 years of age had a negative blood culture before treatment. He recovered promptly and the drug was discontinued. Bacteremia was present in 5 of the remaining 7 patients before treatment was begun and in these patients all subsequent blood cultures were sterile. Two of the 5 bacteremic patients and 1 of the non-bacteremic patients died. In the 4 patients tested, the concentration of the drug in the blood did not reach the desired level in spite of the doses used. In Case 1 the

lower level was obtained while the patient was receiving 3 gm. daily. No toxic effects of the drug was noted in these cases.

It is obviously not possible to draw conclusions from such a small group of cases, but the poor prognosis in the sort of cases selected suggests that the drug may have had some beneficial effect on the disease.

TABLE 8.—RÉSUMÉ OF CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA TREATED WITH A COMBINATION OF SPECIFIC SERUM AND SULPHANILAMIDE (BOSTON CITY HOSPITAL, 1937-38).

Case.	Sex and age.	Blood cultures.	Lobes involved.	Specific serum.		Sulphanilamide.			Termination: mode, day.	Remarks, complications.
				Days.	Units × 1000.	Days.	Total, gm.	Blood,* mg./100 cc.		
1	M 63	Pos. 3, 4, 5; Neg. 6, 7, 8	Ll	4-6	390	4-9	24	7.6-3.3	D9	Emphysema, chronic bronchitis.
2	F 57	Neg. 5, 6, 7, 10	RlLl	6-7	225	6-14	50	8.4	D14	Mild pulmonary edema after serum, then improved; sudden death (no autopsy).
3	M 68	Neg. 6, 7	Rum	6-8	120	6-11	36	6.8	C9	Jaundice and semiconscious before treatment
4	F 67	Pos. 3, 4; Neg. 5	Rl	4-5	R530	4-7	28	...	C6	Chills after 2 doses of serum.
5	M 43	Neg. 4	Ruml	4-5	R500	4	8	...	L5-8	Chill, 2d dose; severe serum sickness.
6	F 55	Pos. 3 (?), 4; Neg. 2, 5-8	Rl	3-6	520	6-8	16	...	D8	Duration uncertain.
7	M 66	Pos. 8; Neg. 6, 10	Rml	8-9	175	8-15	102	6.5	L10-14	Stormy course.
8	F 51	Pos. 2; Neg. 3, 4	Rum	2-3	250	3-8	40	...	C3	Onset with chill 11 days after crisis from Type IX pneumonia treated with sulphanilamide.

* Unheated.¹⁰ The values for the total sulphanilamide were 25 to 50% higher.

ABBREVIATIONS: Sex: M = male, F = female. Lobes: L = left, R = right, u = upper, m = middle, l = lower. Blood cultures: Pos. = positive, N = negative for Type II pneumococci. The numbers represent the day of the disease. Termination: C = crisis, L = lysis, D = death.

Discussion. The low death rate in a comparatively large group of cases of pneumococcus Type II pneumonia during the past 3 years is most encouraging. It is particularly impressive since it was attained, for the most part, with the use of concentrated antipneumococcus horse serums and in spite of the inclusion for specific treatment of an increasing proportion of the Type II cases among which the incidence of bacteremia was high. It will be noted from Table 5 that during the last 3 years, 121 consecutive cases were treated within 96 hours of the onset of the disease with a mortality of 14%. Such a low death rate was previously noted with the use of horse serum preparations by Cecil and Plummer² during a single year in 21 cases admitted within 72 hours of the onset, and in 43 of Bullowa's recent cases (1934-38) treated before the fifth day.¹⁶

The average dose of antibody used in these cases was not high. However, it seems to us that, except where the conditions of the patient precluded the use of larger amounts of the particular lots of serum available at the time, the quantities in individual groups of patients approached more closely than in previous years the

desired ideal in dosage, namely, that amount which is most effective and least wasteful.

The importance of untoward reactions is brought out rather strikingly in these cases. There can be little doubt that some of the individual poor results are ascribable in large measure to this factor. Repeated reactions during serum administration in severely ill patients, particularly when the serum has a low antibody content, are obviously detrimental to the patient. Valuable time is lost, the general defenses of the patient are probably lowered, and one is tempted to use insufficient amounts of the specific agent to be effective.

The results in the small number of cases of pneumococcus Type II pneumonia treated with rabbit serums are encouraging. The fact that the average potency of the rabbit serum preparations used was almost 4 times that of horse serums is most significant. While reactions have been no less frequent, the introduction of larger amounts of the specific antibody with each dose reduces the number of injections necessary to bring about the desired clinical improvement.

Obviously, the most desirable product will be the most potent concentrated antibody that can be given conveniently and with the minimum of untoward effects. The few data presented here and the good results reported from the use of unconcentrated rabbit serums in small groups of Type II cases treated by Horsfall and Loughlin and their associates^{7,9} should encourage further attempts to produce potent concentrated rabbit serums for this type.

The use of sulphanilamide or similar drugs may also prove to be a valuable adjunct to the serum treatment, particularly in bacteremic cases in which treatment is begun late in the disease. They may also be useful in other cases when only serums of low potency are available. Further studies of their use in adequately controlled cases are desirable.

Summary and Conclusions. During the past 3 years, coincident with a steady increase in the proportion of cases treated with serum, the death rate among 148 serum treated cases of Type II pneumococcus pneumonia was 19%. The death rate among 64 contemporaneous non-serum treated cases was 36%; among 196 similar cases occurring since the fall of 1929 it was 42%. Only 14% of 121 cases treated with serum before the end of the fourth day died. The death rates were lower in both bacteremic and non-bacteremic cases. The greatest reduction in mortality appeared to be in patients between 20 and 60 years of age.

The deaths among the serum treated cases occurred chiefly in patients with other serious complicating conditions and in those who were in poor general condition when the treatment was begun.

Untoward reactions to serum injections were more frequent in Type II cases than in the Type I cases. The possible significance of these reactions is discussed.

Concentrated rabbit serums were used in the treatment of 9 patients, including 4 with bacteremia. None of these patients died. The relatively high potency of these Type II rabbit serums suggests that they may prove to be preferable to horse serums in the treatment of pneumococcus Type II pneumonias.

The small experience with sulphanilamide suggests that this or similar drugs may have some usefulness as an adjunct to specific serum in the treatment of certain severe Type II cases.

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SPECIFIC TREATMENT OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIAS.

INCLUDING THE USE OF HORSE AND RABBIT ANTIPNEUMOCOCCUS SERUMS AND SULPHANILAMIDE.

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In the preceding papers^{1,6} we were concerned with the results of specific treatment in the pneumonias due to Types I and II pneumococci. These were the first types to be recognized and are the most frequent causes of pneumonia (with Type III, which is usually somewhat more frequent than Type II). Clinically, they are inti-

mately associated with primary and typical lobar pneumonia and they are rarely found in the nasopharynx of individuals not suffering from or exposed to this disease. Types V and VII are less frequent causes of pneumonia than the three classical types, but they are two of the three most frequent types (Type VIII is the third) classified from among the pneumococci previously included in Group IV.^{3,4} They both differ from Types I and II, as well as between themselves with respect to the character of the pulmonary lesion they may produce and the relative frequency with which they are found in the nasopharynx without relation to pneumonia.^{7,11}

Serums for Types V and VII have come into use only recently and reports concerning their efficacy in the specific treatment of pneumonia are still few, but such reports differ with respect to these two types in about the same manner as the differences concerning the efficacy of Type I and Type II serums. Most writers have had uniformly favorable results in Type V cases, just as in those due to Type I, but the opinions concerning the efficacy of Type VII serums have varied about as much as those concerning the value of serums in Type II cases.^{2,9,12-15,18-20} Only small numbers of cases of the newer types have been included in the reports. The cases occurring at the Boston City Hospital prior to July, 1936, have been reported elsewhere.^{9,12} In both the Type V and the Type VII cases the death rates in serum treated cases were considerably lower than among non-serum treated cases and marked clinical improvement occurred with considerable regularity in direct relation to serum treatment. The results of the past 2 years in a larger number of cases have fully corroborated the earlier experience. For the purpose of brevity, the data concerning the Type V and Type VII cases will be presented in parallel. The comparison between these two types will also bring out certain features of the so-called higher types of pneumococci that are of interest.^{2,5,18}

Patients, Materials and Methods. In general, the choice of patients for treatment with serum or sulphanilamide, the methods of typing and of serum administration were similar to those described for the Type I cases.⁶ Only those aspects that concern the Types V and VII cases specifically will be considered here. For orientation it is well to note, first, what sort of patients harbor pneumococci of these types. Diagnostic serums for Types V and VII have been available at the Boston City Hospital since the fall of 1929 and have been employed in the classification of all pneumococci that have been encountered since that time. The relative frequency with which these types have occurred in patients with pneumonia or with other conditions is shown in Table 1. Most significant is the comparatively high incidence of carriers and persons with simple upper respiratory infections among those harboring Type VII pneumococci as compared with the incidence of those from whom Type V organisms were obtained. In this respect Type V is similar to Types I and II. Equally important is the greater relative incidence of atypical pneumonias in adults. About 19% of the Type VII and 10% of the Type V pneumonias were classed as atypical pneumonias. Moreover, atypical pneumonias associated with Types V and VII pneumococci, particularly the latter, were usually primary,

in contrast to the infrequent cases of atypical Type I or Type II pneumococcus pneumonias which were almost all secondary or terminal events in the course of other serious diseases.

The atypical character of the Type VII cases and the occurrence among them of mild cases, as well as the frequent occurrence of this type in patients without pneumonia has necessitated extra caution in the choice of patients with this type for serum treatment. In those cases in which considerable pulmonary consolidation was not demonstrated and in those whose symptoms were mild, serum treatment was either omitted or postponed until the signs were more evident and the symptoms more characteristic.

TABLE 1.—PATIENTS HARBORING TYPE V AND TYPE VII PNEUMOCOCCI. (BOSTON CITY HOSPITAL, 1929-38).

	Type V.	Type VII.
Lobar pneumonia in adults	298	211
Atypical pneumonia in adults	34	48
Adults admitted with empyema	5	5
Pneumonia and/or empyema in children*	24	4
Focal purulent infections	22	18
Carriers or respiratory infections without pneumonia	8 (2%)	24 (8%)
Total	391	310
Pneumonia in adults:		
Per cent lobar	90.0	81.5
Per cent atypical	10.0	18.5
Per cent of all pneumococcic infections:		
Highest (both in 1935-36)	12.8	8.2
Lowest (V in 1929-30, VII in 1932-33)	3.8	3.6

* Not studied routinely. These cultures obtained from blood, pleural fluids or autopsy material.

Reliability of Direct Neufeld Sputum Typing.^{17,21} In the past 3 years, much reliance has been based on this method for rapid typing. During this period a positive diagnosis of Type V was proved to be incorrect by mouse inoculation of the same sputum in only 4 (5%) of 82 cases in which the comparison was possible. The types of pneumococci obtained from the mouse in these 4 cases were: Types I, II (twice) and III. Likewise a diagnosis of Type VII was incorrect in 2 (3%) of 62 cases; 1 of these proved to have Type I and the other Type V by mouse inoculation. The Neufeld typing with the proper serums was interpreted as negative in 27 (25%) of sputa which yielded Type V and in 20 (23%) of those which later yielded Type VII pneumococci after inoculation into mice. In addition, 2 sputa containing Type V and 4 with Type VII pneumococci were incorrectly diagnosed as other types which were not found by other methods. One of the former was called Type III and the other was called Type VII; and the latter 4 were wrongly diagnosed Types I (2 instances), VIII and IX, respectively.

Therapeutic Serums and Dosage. The data concerning the serum used prior to July, 1936, has been included in the previous reports.^{9,12} Most of the serums used since that time were prepared and furnished for clinical trial by the Lederle Laboratories, Inc. Those employed during the past two years included 25 lots of bivalent Types V and VII concentrated anti-pneumococcus horse serum ranging in potency from 3000 to 7000 units* of Type V and from 4000 to 12,000 units of Type VII antibodies per cc. The concentration of Type V antibody was less than 4000 units per cc. in

* The actual number of units as determined by comparison with the standard serum will be given in the text and tables. The numbers recorded on the labels were 15 to 35% lower.

7 lots, between 4000 and 5000 in 14 and over 5000 units per cc. in 4 lots. For Type VII, there was less than 5000 units of antibody per cc. in 7 lots, between 5000 and 7000 in 11 lots and 7000 units per cc. or more in 7 lots. In addition, 7 monovalent lots of concentrated rabbit serums were used, 1 containing 5500 units of Type V and the others containing from 9000 to 27,000 units of Type VII antibody per cc. Three lots of concentrated Types II and V horse serums, each containing about 1350 units of Type V antibody per cc. and 2 lots of Type VII and VIII horse serums containing 3100 and 4000 units of Type VII antibody were supplied by the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health.

The bivalent Type V and VII serums were usually given as follows: an initial 5 cc., 2 hours later a second dose of 15 or 20 cc. (occasionally 35 cc.) and, if necessary, 20 to 40 cc. 2 or more hours later, depending on the age of the patients and the other factors already mentioned as indicating larger doses.⁶ With the other horse serums and with the rabbit serums, which were mostly experimental lots, the initial injection was 1 to 2 cc. followed, at intervals of 2 hours or more, by increasing amounts depending on the occurrence and severity of reactions. All were given intravenously, except some of the doses of rabbit serum which were given intramuscularly.

Results. Gross Mortality. The death rates among the cases of each type varied from year to year but were constantly much lower for the serum treated than for the non-serum treated cases. This difference persisted even in the last year when a considerably larger proportion of the cases were treated with serum as compared to previous years. The figures for the different years during which these serums have been available are shown in Table 2.

TABLE 2.—MORTALITY IN CASES OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIA (BOSTON CITY HOSPITAL, 1929-38).*

Years.	Type V cases.							Type VII cases.						
	Serum treated.			Non-serum treated.			Serum treated, %.	Serum treated.			Non-serum treated.			Serum treated, %.
	No.	Died.	Died, %.	No.	Died.	Died, %.		No.	Died.	Died, %.	No.	Died.	Died, %.	
1929-33	116	50	43	0	..	4	0	56	14	25	0
1933-34	7	..	0	0	21	7	33	16
1934-35	7	..	1	14	9	4	44	44
1935-36	26	4	15	65	24	37	28	19	2	11	28	9	32	40
1936-37	23	1	4	42	20	48	35	14	2	14	33	7	21	30
1937-38	32	3	9	11	3	27	74	35	4	11	13	6	46	73
Total . .	81	8	10	234	97	41		79	9	12	160	47	29	

* In this table and in those that follow, all cases receiving specific serum are included regardless of the amount or the time given. From among the non-serum treated cases are excluded those in whom the pneumococcus was first identified from autopsy materials. The numbers of such cases for the various periods are: among the Type V cases: 1929-35, 14; 1935-36, 2; 1936-37, 3 (total, 19 cases); among the Type VII cases: 1929-33, 7; 1934-35, 2; 1935-36, 7; 1936-37, 3; 1937-38, 1 (total, 20 cases).

Influence of Bacteremia. In both the Type V and the Type VII cases the death rate was about 5 times as high among the patients with positive blood cultures as among those whose blood cultures

showed no growth. This was true for both the serum treated and the non-serum treated cases. The differences in death rates between the cases receiving serum and those not treated with serum was equally striking in both the bacteremic and non-bacteremic cases of each type. These death rates are shown in Table 3.

TABLE 3.—EFFECT OF BACTEREMIA ON THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIA (BOSTON CITY HOSPITAL, 1929-38).

Result of blood culture.	Type V cases.						Type VII cases.					
	Serum treated.*			Non-serum treated.			Serum treated.*			Non-serum treated.		
	No.	Died.	Died, %.	No.	Died.	Died, %.	No.	Died.	Died, %.	No.	Died.	Died, %.
Positive	27 ¹	6	21	84	67	79	16 ²	6 ¹	38	32	28	88
Negative	54 ¹	2	4	111	17	15	63 ⁷	3	5	102	16	16
Not done	39	13	33	26	3	12
Bacteremic, % . . .	33			43			20			24		

* The superscripts indicate the number of cases treated with rabbit serums.

The cases in which multiple blood cultures were done during the acute disease or before beginning serum treatment are of interest. Those occurring before 1935 have been noted previously^{7,11} and the recent ones are summarized in Table 4. The importance of making

TABLE 4.—RESULTS OF MULTIPLE BLOOD CULTURES TAKEN DURING THE ACUTE DISEASE AND BEFORE SERUM TREATMENT (1935-38).

	Type V cases.				Type VII cases.			
	Serum.		No serum.		Serum.		No serum.	
	Recovered.	Died.	Recovered.	Died.	Recovered.	Died.	Recovered.	Died.
More than 1 blood culture positive	10*	2	2*	10	0	2	0	2
First blood culture sterile, later ones positive	3	1	2	2	4	0	1*	1
All blood cultures sterile	23	0	13	3	21	2	9	5
First culture positive, later ones sterile	1	0	2	3	1	0	0	1

* One case developed empyema.

a blood culture immediately before the first dose of serum is given regardless of whether previous cultures have been made is apparent from these results. Bacteremia developed under observation in 14 cases of both types. Serum was given after the bacteremia developed in 8, of whom only 1 died, whereas of the 6 who did not receive serum, 3 died. Most significant, however, is the small

number of deaths among the Type V cases who had more than one positive blood culture and then received serum as compared with the large number of similar cases who died without receiving serum.

Influence of Age (Table 5). Deaths in patients under 20 years of age did not occur among the Type VII pneumonias and were

TABLE 5.—DEATH RATES IN CASES OF TYPE V AND VII PNEUMOCOCCUS PNEUMONIA ARRANGED ACCORDING TO AGE (BOSTON CITY HOSPITAL).

Age group, yrs.	Type V cases.						Type VII cases.					
	Serum treated, 1935-38.			Non-serum treated, 1929-38.			Serum treated, 1933-38.			Non-serum treated, 1929-38.		
	No.	Died.	Died, %.	No.	Died.	Died, %.	No.	Died.	Died, %.	No.	Died.	Died, %.
12-19	19	1	5	30	1	3	8	0	0	16	0	0
20-29	18	0	0	32	11	34	17	0	0	25	1	4
30-39	25	4	16	58	18	31	21	2	9	26	3	11
40-49	13	1	8	44	21	48	15	1	7	33	15	45
50-59	4	1	25	37	21	57	12	3	25	31	12	39
60+	2	1	50	33	25	76	6	3	50	29	16	55
Total	81	8	10	234	97	38	79	9	12	160	47	29

rare in the Type V cases. In older patients, the death rates were lower among those receiving serum than among the non-serum treated cases. Relatively few patients over 60 years were treated with serum. The number of treated cases in the various age groups is too small to indicate the full effect of age on mortality as was shown among the serum treated Type I and II cases^{1,6} and in the present non-serum treated cases.

Influence of the Time When Serum Treatment Was Begun. The importance of early treatment is indicated by the death rates for cases treated on various days after the beginning of the pneumonia as shown in Table 6. Treatment with serum was equally effective,

TABLE 6.—INFLUENCE OF THE DURATION OF THE DISEASE AT THE TIME SERUM TREATMENT IS BEGUN ON THE DEATH RATES IN CASES OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIA (BOSTON CITY HOSPITAL).

Day treatment begun.	Type V cases.*			Type VII cases.*		
	No.	Died.	Died, %.	No.	Died.	Died, %.
Fourth or earlier . . .	67 ²⁰	5 ³	7	60 ⁸	2 ¹	3
Fifth	7 ²	0	0	9 ²	0	0
Sixth	3 ²	1 ¹	33	5 ¹	2	40
Seventh and later . .	4 ³	2 ²	50	5 ⁵	5 ⁵	100

* The superscripts represent the number of bacteremic cases included.

insofar as indicated from the low death rates, when treatment was begun on or before the fifth day. The cases treated after that time are too few to be highly significant, however, particularly since patients seen later in the disease were generally not treated with serum if they appeared to be improving and the results of blood

cultures were known to be negative. The fatalities occurred primarily in the late bacteremic cases.

Dosage. The average doses of antibody used are analyzed in Table 7. The concentration of antibodies in terms of units was considerably greater in the Types V and VII serums than in those for Types I and II. This permitted the administration of much larger amounts of antibody, in a smaller total volume, and with fewer injections. Since the units of antibody are based on protection of mice against the specific organisms the unit for any one type of pneumococcus is not necessarily comparable in its therapeutic

TABLE 7.—SUMMARY OF THE AVERAGE DOSES OF SPECIFIC ANTIBODY USED IN CASES OF TYPE V AND TYPE VII PNEUMOCOCCUS PNEUMONIA AT THE BOSTON CITY HOSPITAL.

	Type V. (81 cases*).	Type VII.	
		Horse serums (70 cases).	Rabbit serums. (9 cases).
Volume (cc.)	43	39	43
Units† (thousands)	150	209	530
Units per cc.	3490	5360	12,300
Number of injections	3.4	3.2	3.2
First injection (thousands of units)	17	25	12
Subsequent injections	55	84	235‡
Total dose per patient:			
Non-bacteremic cases	116	173	360
Bacteremic cases	219	264	1130
Recovered cases	147	195	480
Fatal cases	162	319	1260
Age: Less than 30 years	131	185	225
30-49 years	157	215	585
50 years and older	205	224	930
Average age (years)	31.4	37.6	39.2

* Nine patients were treated with some of the first lots of this type prepared by the State laboratory. The average dose in these patients was 127 cc., containing 231,000 units (1835 units per cc.) in 6.8 injections. If these cases are omitted the average dose in the remaining cases was 32 cc., containing 140,000 units (4375 units per cc.) given in 3 injections. Concentrated rabbit serums were used in 2 Type V cases, including 1 bacteremic patient. Each received 17 cc. containing 85,000 units in 2 injections. (See footnote p. 383.)

† Compared with standard serum L1, maintained by the Lederle Laboratories, Inc., to which was assigned a value of 150 units of Type V and 300 units of Type VII antibody per cc.

‡ The intramuscular route was used to give virtually the entire dose in 2 patients and part of the dose in 2 others.

efficacy in man to that of any other type. However, the use of standard serums in the evaluation of the potencies permit, within any given type, the most uniform comparison that can be made with the available methods. Larger doses, in terms of these units, were necessary for Type VII than for Type V cases, but the serums were proportionally more concentrated. As with other types, larger doses were used in bacteremic and in older patients.

Untoward Reactions. The various types of untoward reactions observed following serum therapy in both the Type V and the Type VII cases were similar in character and frequency to those

observed in the serum treated Type I case.⁶ They are listed in Table 8.

The reactions classed as "immediate" occurred during the injection or at varying intervals up to 1 or even 2 hours later. About one-half of them were associated with the initial injections, while some occurred only after 2 or more uneventful injections. Only 2 patients experienced such reactions after each of 2 or more injections. In 2 patients who were almost moribund when treatment was begun, death followed within a few minutes of an injection (the second and sixth, respectively). All the thermal reactions were mild or moderate. Only 2, each following injections of experimental lots of rabbit serum, were followed by fever of 106° F., or higher, and these responded promptly to treatment. Serum sickness was mild in most cases and moderate in a few. Fever to 100° or 101° F. accompanied the urticaria and arthralgia in most, but not all, of the cases.

TABLE 8.—OCCURRENCE OF UNTOWARD REACTIONS IN PATIENTS WITH TYPE V AND TYPE VII PNEUMOCOCCUS PNEUMONIAS TREATED WITH SPECIFIC ANTIBODY (BOSTON CITY HOSPITAL).

	Type V. (81 cases).	Type VII.	
		Horse serums (70 cases).	Rabbit serums (9 cases).
Immediate reactions	11 (14%)	12 (17%)	2
Nausea and/or vomiting	3	3	
Urticaria	5	2	
Dyspnea, cyanosis, asthma	1	5	
Fainting (collapse)	1	1	1
Chill during injection	1	1	1
Thermal reactions	21 (26%)	6 (9%)	5
After 1 injection only	16	6	3
After 2 or more injections	5*	0	2
Only after the first injection	4	1	1
After first and later injections	3*	0	2
Only after second and/or later injections	14	5	2
Delayed serum sickness	21 (26%)	23 (33%)	1
Fever only	2	2	
Urticaria	3	5†	
Arthralgia	11†	9	
Arthralgia and urticaria	5	7	1

* Including 1 rabbit serum recipient.

† Includes 1 with adenopathy in addition.

Clinical Response. Prompt crisis followed serum treatment in most of the cases. Among the 68 Type V cases who recovered without purulent complications, 48 (71%) had a crisis within 24 hours and only 3 were ill more than 48 hours after the first injection of type specific antibody. Only 14 (21%) of the corresponding non-serum treated cases were clinically improved within 24 hours after admission to the hospital.

Among the Type VII cases, 45 (64%) of those who recovered had a crisis within 24 hours and 8 (11%) more were afebrile within 48 hours of the first dose of serum. In some of the remaining patients there were mixed infections, but in 10 of the cases, including the 2 who received the entire dose of rabbit serum intramuscu-

larly, the course of the disease was not demonstrably influenced by what were considered to be moderately large doses of antibody, and no cause for these possible failures was detected.

Complications. Purulent complications were demonstrated after serum treatment in 8 (10%) of the Type V cases. They included empyema 5, bilateral otitis media 1, and pelvic abscess 1. Only 1 of these patients died and vegetative endocarditis was found in addition to the empyema in this patient. Three of the patients with empyema and the one with the pelvic abscess had positive blood cultures before treatment was begun. Serofibrinous pericarditis was demonstrated in 1 of the fatal serum treated patients who had active rheumatic heart disease. Among the contemporaneous non-serum treated Type V patients 15 (12%) had empyema and 11 of them died. In 6 of the 11 fatal cases, other complications were also found, including endocarditis in 3, and pericarditis, meningitis and lung abscess, each in 1 case. One additional patient had rheumatic heart disease and was found to have vegetative endocarditis at autopsy. There were 8 pregnant women among the serum treated patients, including 3 who died during or after miscarriage, and 1 who developed empyema and whose pneumonia probably began during or just before a normal delivery. The pregnancy proceeded uneventfully into convalescence in the other 4 patients. One of the non-serum treated patients died soon after the premature delivery of a normal live baby.

Purulent complications were relatively uncommon among the Type VII patients. Meningitis was present on admission in 1 of the serum treated patients and autopsy disclosed, in addition, the presence of vegetative endocarditis. The latter was probably also present in 2 other patients who had persistently positive blood cultures and developed cardiac murmurs after serum treatment, but there were no embolic phenomena recognized and no autopsies obtained in these patients. Frank empyema developed in 2 non-serum treated patients and meningitis in 1; the latter and 1 of the former died.

Serofibrinous effusions which resorbed spontaneously were demonstrated in 3 serum treated and in 2 non-serum treated Type VII patients who recovered. In 1 of the former, organisms resembling pneumococci were seen in smears of the first fluid, and in 1 of the latter Type VII pneumococci were cultured from the first fluid withdrawn. In 1 of the serum treated patients, a 7 months' pregnancy was unaffected, whereas 1 of the non-serum treated patients miscarried a 3 months' fetus before crisis.

Fatal Cases. The essential details concerning the serum treated patients who died prior to July, 1936, have been recorded elsewhere.^{9,12} Death in each instance was associated with late or inadequate treatment or with serious complicating factors. The same was true during the past 2 years.

Of the 4 recent fatal serum treated Type V cases, 3 were bacteremic and in extremis when the first dose of serum was given and lived only a few hours thereafter. One of them had rheumatic heart disease and auricular flutter, and autopsy disclosed a vegetative endocarditis. The fourth patient was 4 months pregnant and developed increasing pulmonary edema following serum administration and died 2 days later during labor. The blood culture on the day of death showed hemolytic streptococci.

Among the serum treated Type VII patients who died during the last 2 years, 1 had meningitis on admission and autopsy revealed endocarditis in addition. Two patients in whom serum treatment was begun late in the disease continued to have positive blood cultures following large doses of serum and endocarditis was suspected but no autopsies were obtained.

TABLE 9.—RÉSUMÉ OF RELEVANT DATA IN CASES OF TYPE V AND TYPE VII PNEUMOCOCCUS PNEUMONIA IN WHICH SULPHANILAMIDE WAS USED.

Case	Type.	Sex and age.	Blood cultures.	Lobes involved.	Specific serum.		Sulphanilamide.			Termination: mode, day.	Remarks.
					Days.	Units \times 1000.	Days given.	Total gm.	Mg./100 cc. in blood.*		
1	V	F 30	Pos. 1; Neg. 2, 3, 5	Lu	2-4	320	5-7	16	...	C6	Sore throat 4th day.
2	V	M 14	Neg. 4	Rl	11-20	33	...	L22	S.H. in sputum and in 4 pleural fluids; anemia; transfusion 500 cc. on 18th and 24th days; no operation.
3	V	M 46	Pos. 6; Neg. 8, 9, A	Ruml	6-9	27	...	D9	S. aureus and H. influenzae (no pneum.) found at autopsy.
4	VII	F 19	Neg. 4, 8, 10, 12	RlLl	4-7	560	9-14	24	6.0	C13	S.H. and Pn. VII in sputum 10th day.
5	VII	M 52	Pos. 9, 11, 12, 13, 14, 15	Ruml	11-14	420	13-15	20	7.5	D15	Pericardial rub and systolic murmur 14th day.
6†	VII	F 43	Pos. 28 (?), 29, 30, 31, A	Ru	29-31	530	26-31	42	4.6; 5.1	D32	Meningitis and endocarditis.

* The levels after heating were 1 to 2.5 mg. higher.¹⁶

† The details in this case and another case of meningitis without pneumonia are recorded elsewhere.¹⁰

ABBREVIATIONS: Sex: M = male, F = female. Lobes: R = right, L = left, u = upper, m = middle, l = lower. Blood cultures: Pos. = positive, Neg. = negative for the homologous type of pneumococcus, the numbers represent the day of disease, A = autopsy culture of heart's blood. Termination: C = crisis, L = lysis, D = died. Remarks: S.H. = hemolytic streptococci.

A fourth patient with uremia (100 mg. non-protein nitrogen per 100 cc. of blood before serum treatment) died 24 hours after serum was given. The fifth patient, a 56-year-old colored man, had a growth of about 4000 colonies of Type VII pneumococci per cc. of blood before treatment, which, according to the history, was undertaken on the second day. He was in very poor condition and died during the second injection of serum. The sixth fatal case was a 64-year-old man with bacteremia and auricular fibrillation who was treated with rabbit serum on the fourth and fifth day of illness. He was considerably improved but died suddenly while attempting to get out of bed 5 days later.

Résumé of Cases Treated With Rabbit Antipneumococcus Serums. Concentrated type-specific rabbit serums were used in the treatment of 2 cases of Type V and 9 of Type VII pneumococcus pneumonia. The 2 Type V patients were 14 and 20 years of age, respectively.

The latter had a positive blood culture before treatment. Each received 85,000 units in 2 injections and recovered promptly. A chill occurred after each dose in 1 of the patients. Among the Type VII patients 2, including the 1 fatal case, had positive blood cultures. Large amounts of antibody were given (see Table 7). Chills occurred in 5 patients and necessitated administration by the intramuscular route for part or almost all the serum in 4 patients. One patient had a marked drop in blood pressure and "collapse" following an intravenous dose. Serum sickness developed in only 1 patient (see Table 8). The 2 patients who received practically all their serum intramuscularly were acutely ill for 4 or more days after treatment, whereas 5 of the 6 remaining patients who recovered had a crisis within 12 hours and the sixth within 22 hours after the first injection of serum.

Sulphanilamide. The significant data in 6 cases treated with the drug alone or with specific serum are shown in Table 9. In general, the drug was used only in cases with complicating hemolytic streptococcal infections or when bacteremia occurred late in the disease. In Case 2, the hemolytic streptococcal empyema was treated by repeated thoracentesis and did not require other operative interference. In Case 3, no pneumococci could be recovered from the lungs at autopsy, although they were cultured from the blood 3 days previously, before any of the drug had been given. The data in Case 5 and Case 6 would indicate that the bacteriostatic action is not adequately effective with bacterial endocarditis, at least with the doses of the drug used.

Discussion. The results presented in this paper indicate the sort of effects that specific serums may be expected to yield in the treatment of cases of pneumonia due to the so-called "higher types" of pneumococci. The Type V cases represent a group in which the organism is definitely related to the pulmonary infection with great regularity, just as in cases with Types I and II pneumococci. The specific serums for Type V are potent and uniformly effective. The failures are definitely accounted for by causes apart from the specific action of serum.

Type VII pneumococcus, on the other hand, represents a type which like Type III^{5,8} may be present frequently in sputum or pharyngeal cultures when there is no pneumonia present or where there is only a simple infection of the upper respiratory tract. Under such conditions the finding of this organism in any given case of pneumonia may be misleading and may mask the true etiologic agent. Treatment directed against this organism under such circumstances will be of no avail, as indicated in a number of the recent cases. When the organisms are found regularly, in large numbers as the only apparent agent, the disease should be favorably influenced by specific serum. Other causes residing in

the organism, the serum, or the patient may be responsible for some of the failures, but these have escaped detection.

It was shown elsewhere¹¹ that the immunologic reactions of the serum of patients with Type VII pneumococcus pneumonia differ from those of the other types, including Type V,⁹ in that high titers of protective antibodies can be demonstrated for the homologous type during the acute disease. Mouse protective antibodies for Type VII pneumococci may also be demonstrated in normal adults.¹¹

The results of treatment with specific antipneumococcus rabbit serums were similar, in general, to those obtained with corresponding horse serums. The number of cases, both these and the ones included in other recent reports^{13,15} are too few to draw conclusions concerning the relative merits of the one over the other.

Sulphanilamide was not used in these cases in such a manner as to demonstrate its efficacy as a curative agent. In the present state of our knowledge concerning this or similar drugs, it is best to limit their use, when effective specific agents are available, to those cases in which the conditions are not favorable for the most effective use of the specific agent. These include late bacteremic cases or those with mixed infections or superinfections, and in such cases it is best used to supplement specific serum therapy. It is probably most effective in complicating hemolytic streptococcal infections.

Summary and Conclusions. The experiences with specific serums in 81 cases of Type V and in 9 cases of Type VII pneumococcus pneumonias treated at the Boston City Hospital prior to July 1, 1938, are presented.

Among the 81 Type V cases treated in 1935-38, the death rate was 10% as compared with 41% deaths among 234 non-serum treated cases, which included contemporary cases and those occurring in the 6 years before the introduction of specific serum. Following serum treatment clinical improvement was rapid and complete. Deaths occurred only when specific treatment was undertaken in the face of severe complicating conditions or when it was begun after the fifth day in bacteremic cases. Purulent complications probably developed less frequently after specific treatment.

The death rate among the 79 serum treated Type VII cases was 12% as compared with 29% among 160 earlier and contemporaneous non-serum treated cases. Although the results of serum treated were similar, in general, to those obtained in Type V cases, there was an appreciable number of cases in which the serum did not seem to influence the course of the disease and the cause of these failures was not identified. Type VII cases were more frequently atypical and, because this type is relatively frequent in sputum or in pharyngeal cultures of patients without pneumonia, added caution is required in the choice of proper cases for specific treatment.

The serums used for both these types were highly potent. Un-

toward reactions and serum sickness were relatively infrequent. Concentrated antipneumococcus rabbit serums were used in 11 patients. The data in these cases indicate that the rabbit serums are probably equally as effective as the horse serum preparations. More data are necessary to determine any superiority of the one over the other. Likewise too few cases have been treated with sulphanilamide to evaluate the place of this drug in the treatment of pneumococcus pneumonias of these types.

The authors are indebted to the members of the staffs of the various medical services and of the Mallory Institute of Pathology for their most generous coöperation in this study and to the Lederle Laboratories, Inc., and the Massachusetts Antitoxin and Vaccine Laboratories for the supply of serums and the data concerning them.

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THE PERSONALITY TYPE OF PATIENTS WITH TOXEMIAS OF LATE PREGNANCY.

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It would seem at the outset that a study of psychic make-up would be totally unrelated to the investigation of a group of diseases which are so obviously on a physical basis. The ultimate solution of the etiology of eclampsia and preëclamptic toxemias, however, must rest upon the accumulation of a multitude of facts. It would be fitting to study eclamptogenic toxemias in relation to

certain other hypertensive states in which there are known differences of personality.

It is widely accepted that there is a constitutional type of woman apparently predisposed to the development of the toxemia syndrome in late pregnancy. Clinical observation²⁻⁴ has shown that women who are shorter, heavier, and stockier than usual, and who, in the authors' experience, often reveal such stigmata of endocrine dysfunctions as hypertrichosis, prognathism, android or masculine type of pelvis, and peculiar fat distribution show a higher incidence of late toxemias than the tall, slender, asthenic type.

The cardinal sign of the toxemias of late pregnancy is an elevated blood pressure. While the exact mechanism of this hypertension is not known, we are fairly certain that the immediate mechanical cause is an increased peripheral resistance due probably to a generalized increase in arteriolar tonus. In this respect, it resembles the disease commonly referred to as essential hypertension, which also appears to affect a particular group of individuals. Ayman¹ summarizes the literature regarding the characteristics of these persons afflicted with arteriolar essential hypertension, and in a controlled study determined that they possess a distinct psychic make-up. "Their personality is characterized by increased psychomotor activity. They are dynamic, hyperactive individuals with a large and steady output of energy. They tend to be sensitive and quick-tempered. . . . The hypertensive personality has existed as far back as the subject can remember." It is not to be presumed that such personality types play a rôle in the actual causation of the hypertension, nor that the hypertension alters the personality. Ayman believes that both factors are the result of a common hereditary or physical cause, perhaps endocrine in nature.

The methods used by Ayman were duplicated as closely as possible in the present study in an attempt to answer the following questions: Do women who develop preëclampsia or eclampsia also possess a hypertensive personality? Is there any evidence of a life-long "autonomic imbalance" as reflected by the mental traits and habits of such women? Could such tests prove of value in differentiating preëclamptic toxemia from essential hypertension in pregnancy?

Clinical Material. The clinical material used in this study is comprised of 148 women, all of whom were bed patients on obstetrical wards. The classification of the hypertensive group used throughout is one which has been developed by one of us in this hospital and used exclusively during the past few years. It is based on the probable origin of the elevated blood pressure rather than on symptoms or on urinary findings which are less constant than hypertension in the late toxemias of pregnancy. Any patient presenting a persistent elevation of blood pressure over 140 systolic or 90 diastolic (on three or more determinations at least 1 hour apart)

was placed in this "hypertensive group." Ninety-seven such patients were carefully studied for several days before establishing the final diagnosis. If the diagnosis was still in doubt at the end of the puerperium, the personality inventory was excluded from the present study.

While it is not the purpose of this report to discuss the diagnosis and classification of the late toxemias, it should be mentioned that the routine investigation of any case included the measurement of the blood pressure at least twice daily; a quantitative estimation of albuminuria daily; a quantitative urinary sediment count when abnormal urinary elements were found; examination of the ocular fundi; determinations of non-protein nitrogen, urea, uric acid, and in doubtful cases the urea clearance, blood sugar and carbon dioxide-combining power; and the response of the blood pressure to physical (cold) and psychic (fright) stimuli in selected cases. Particular attention was paid to the prenatal blood pressure record, the behavior of the blood pressure in previous pregnancies and the family history of hypertension and cardiovascular disease. Such patients were then classified as follows:

GROUP I (46 patients). *Preëclamptic toxemia*, defined as that syndrome appearing in the latter half of pregnancy among women previously normal, characterized by hypertension, albuminuria, and certain subjective symptoms, and which, if progressive, may lead to eclampsia. The cases were actually subdivided into mild, moderate and severe grades, although for the purpose of this study such subdivision was not made.

GROUP II (16 patients). *Chronic vascular-renal disease following known previous preëclamptic or eclamptic toxemias*. This group, often referred to as "recurrent toxemias," warrants segregation for several reasons. It consists only of multiparæ who have records of previous preëclampsia or eclampsia and who show a recurrence of hypertension and albuminuria with succeeding pregnancies. Histologic studies of the kidneys from such cases have revealed a type of permanent glomerular damage quite distinct from the chronic glomerulonephritis which develops apart from pregnancy. Clinically, the hypertension may be out of all proportion to the degree of albuminuria or toxic symptoms.

GROUP III (16 patients). *Eclampsia*, defined as a preëclamptic toxemia with the addition of convulsions or coma or both.

GROUP IV (8 patients). *Hemorrhagic Bright's disease* (chronic glomerulonephritis) complicating pregnancy, but definitely antedating pregnancy. (Combined with Group II for this study.)

GROUP V (11 patients). *Essential (arteriolar) hypertension complicating pregnancy*. In these cases the hypertension usually began before or very early in pregnancy and persisted following the puerperium. There were few, if any, subjective symptoms and rarely more than a trace of albumin (although occasionally the full

syndrome of preëclampsia would suddenly be superimposed upon this basic picture as the patient approached term). The blood pressure showed excessive lability to stimuli. Blood analysis values were all within normal limits. There was frequently a familial history of hypertension. These cases were segregated through careful investigation from Groups I, II and IV.

In addition to the above patients, a group of 51 normal pregnant women were studied under identically the same conditions. Blood pressures were taken with mercury sphygmomanometer and auscultation on admission (before bed rest), during labor and at least once during the puerperium. The patient was excluded as a control if any readings exceeded 140 systolic or 90 diastolic. The only factor entering into the selection of these controls was the age of the patient for it was desired to have the same mean age and age distribution in the control group as in the hypertensive group.

Table 1 gives data regarding the age, parity, prenatal care, height, weight and weight gain with pregnancy for each group.

Method of Present Study. A set of questions identical with those developed by Ayman was used (see list of questions below) and the same method of questioning applied.

TABLE 1.—AGE, PARITY, PRENATAL CARE, HEIGHT, WEIGHT, AND WEIGHT GAIN WITH PREGNANCY OF EACH GROUP STUDIED.

Group.*	No. of cases.	Mean age.	Primipara, %.	Average No. mos. prenatal care.	Mean height.	Mean weight (non-pregnant) in lbs.	Mean weight gain with pregnancy.
N	51	26.5	32	3.7	5'4"	120	21
I	46	26.0	60	2.9	5'2"	124	29
III	16	25.0	55	3.6	5'3"	130	32
II and IV	24	34.0	8	3.7	5'5"	143	27
V	11	30.0	10	3.1	5'5"	140	19

* N = Normal pregnancy.

I = Preëclamptic toxemia, all grades.

III = Eclampsia.

II and IV = "Recurrent toxemias" and chronic nephritis in pregnancy.

V = Essential hypertension in pregnancy.

It may be noted upon comparison of the results of this study with that of Ayman that the percentage of positive answers among the control group and the essential hypertension group are, with few exceptions, consistently higher in the present study. Since the evaluation of the patient's personality traits as judged by the answers to these questions varies considerably with different observers, this difference in interpretation may be partially accounted for. It is also apparent that all patients in this series are women whereas about three-fourths of Ayman's patients were men, and this may account for some difference in the subjective evaluation of certain traits. The fact that all had just passed through a period of pregnancy may have unavoidably influenced the answers. It is possible, for example, that women may more readily admit being unusually sensitive, more easily "excited within themselves," more easily embarrassed, or more susceptible to blushing, for it cannot be denied that such traits are often thought to be "feminine weaknesses" and falsely denied by males. For these reasons, the numerical results of the present report are not strictly comparable with those of the preceding study, being consistently higher throughout.

The complete list of questions utilized is as follows:

1. In general, throughout your life, not on any one special occasion and compared with the average person of your own age with whom you have come in contact, have you been of an unusually high-strung or of a calm nature?

2. In general, etc. . . . (as in Question 1) have you been the sort of person who loses his temper quickly (who flies off the handle easily over little things), or has it usually required a good deal to make you lose your temper?

3. In general, etc. . . . have you been the sort of person who, even if you don't show it externally, feel yourself frequently getting all excited over little things?

4. In general, etc. . . . have you been the sort of person whose feelings are unusually easily hurt, who is unusually sensitive, or does it take a great deal to make you feel hurt?

5. As a younger person, did you or do you still blush or flush unusually easily, compared with the average person of your age? Would people "kid you about it"?

6. As a younger person did you, or do you still become unusually easily embarrassed compared with the average person?

7. In general, etc. . . . (as in Question 1) have you been the sort of person who worries unusually easily over little things, or have you tended to pass them over?

8. In general, etc. . . . have you been of an unusually serious nature or of a happy-go-lucky nature?

9. In general, etc. . . . have you been of an unusually forward or unusually shy nature?

10. In general, etc. . . . have you ever had frequent nosebleeds?

11. In general, etc. . . . have your hands or feet tended to become easily cold on slight changes of weather?

12. In general, etc. . . . have you tended to walk at an average pace, slower than the average person, or definitely faster than the average person?

13. In general, etc. . . . have you tended to work at an average pace, slower than the average person, or definitely faster than the average person?

14. In general, etc. . . . have you tended to eat or talk at an average rate, slower than the average person with whom you eat (or talk) or faster than the average person?

15. In general, etc. . . . have you been of average, less than average, or more than average physical activity?

Only definite replies were used. A doubtful response was never counted as a positive answer to that particular question.

Results. The results of the questioning are presented in Table 2. It is readily apparent that the incidence of a familial history of hyper-

tension among Group V (essential hypertension) is three times that of the control group. In Groups II and IV the incidence is also increased, but less than twice, while in the true toxemias of pregnancy (Groups I and III) the differences are hardly significant.

TABLE 2.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS OF EACH GROUP STUDIED, AND THE INCIDENCE OF FAMILIAL HYPERTENSION.

Group.*	Number of cases.	Family history of hypertension (%).	1. Highstrung.	2. Quick-tempered.	3. Easily excited within themselves.	4. Sensitive.	5. Blush easily.	6. Easily embarrassed.	7. Easily worried.	8. Unusually serious.	9. Unusually shy.	10. Frequent epistaxis.	11. Hands or feet easily cold.	12. Fast walker.	13. Fast worker.	14. Fast talker or eater.	15. Unusually active physically.	Average of all positive answers.
N . . .	51	24	18	30	28	68	50	40	30	30	52	14	32	36	38	20	56	36
I . . .	46	26	35	33	54	63	45	37	48	39	54	6	28	24	22	19	52	38
III . . .	16	38	19	44	12	62	50	44	50	50	44	6	31	25	25	19	44	35
II and IV	24	42	16	32	48	64	24	40	40	32	64	8	24	56	48	16	64	38
V . . .	11	73	91	36	91	100	45	36	100	73	91	9	63	45	63	27	91	64

* N = Normal pregnancy.

I = Preëclamptic toxemia, all grades.

III = Eclampsia.

II and IV = "Recurrent toxemias" and chronic nephritis in pregnancy.

V = Essential hypertension in pregnancy.

In analyzing the results it is seen that over 90% of the patients in Group V stated that they were highstrung, easily excited within themselves, unusually sensitive, easily worried, unusually shy, or unusually physically active. In no other group did over 68% give positive answers to any one of the 15 questions, and in most instances less than half gave positive replies to the questions to which Group V gave 91 to 100% affirmatives. These differences are so marked that they must be considered significant.

In comparing Groups I, III, II and IV with the control group, it is found that the results of questioning vary rather widely in both directions, as one might anticipate in dealing with such data, but there is no consistently higher trend over normal for any of these groups. This may be illustrated in another way by averaging all of the percentages for each group. Such an average *per se* is meaningless except as a basis for comparison. The figures are shown in the column to the extreme right in Table 2. The average for the control group is 36%; for the preëclamptic group 38%; for eclampsia 35%; for recurrent toxemias and nephritis 38%; and for essential hypertension 64%. Only in the last group is this average significantly altered from the normal.

This would indicate that the women with preëclampsia, eclampsia, or nephritis do not differ in these personality traits from normal pregnant women, while essential hypertension does seem to be associated with a more "hypertensive personality."

Discussion. The statistical data given in Tables 1 and 2 indicate that preëclampsia and eclampsia occur more frequently with first pregnancies (as is well known), while nephritis and essential arteriolar hypertension are manifest most commonly in multiparæ; that the weight gain with pregnancy is greater than normal with the true toxemias, and normal or below normal with essential hypertension; that women with true pregnancy toxemias or nephritis have essentially the same personality traits as the normal group, and show no special familial diathesis for hypertension, while women whose pregnancy is complicated by essential hypertension give a family history of hypertension in three-fourths of the cases, and show a definite tendency to increased psycho-motor activity.

It should be emphasized that any differences shown between the various groups are not considered to be of any etiologic importance. The results suggest the possibility, however, that there is some relationship between the nervous system and the mechanism of hypertension in essential hypertension which is not present in the toxemias of late pregnancy.

The differential diagnosis among women showing hypertension in late pregnancy is difficult and at times impossible. No single sign or symptom can be relied upon to classify such cases; nevertheless such classification is highly desirable from the standpoint of prognosis, treatment, and academic research. In the authors' opinion, the classification briefly outlined above is as close to an etiologic grouping as our present knowledge allows. The differences in the personality types of the individuals as demonstrated in the present study, and the differences in the constitutional types as demonstrated so well by other writers⁴ should be utilized along with all the other findings of the history and examination in arriving at the proper classification.

Summary and Conclusions. 1. A method used by a previous worker in the study of non-pregnant individuals with essential hypertension has been utilized to study the personality types of women with normal pregnancies, and with pregnancies complicated by preëclamptic toxemia, eclampsia, glomerulonephritis, or essential hypertension.

2. The results indicate that only those women with essential arteriolar hypertension (as a group) differ significantly from the normal in having personalities characterized by an increased psycho-motor activity.

3. Further correlations are shown between the diagnosis and the age parity, height, weight gain with pregnancy and family history.

A classification based on the probable origin of the hypertension is suggested for use.

4. The relationship between the hypertensive personality and the late toxemias of pregnancy with its value in differential diagnosis is discussed.

The writers wish to express their thanks to Drs. L. L. Emmons and H. A. Tanton for their assistance in the compilation of data.

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BOOK REVIEWS AND NOTICES

PRACTICAL OTOTOLOGY. By MORRIS LEVINE, M.D., F.I.C.S., Clinical Professor of Oto-laryngology, New York Post-Graduate Medical School, Columbia University; Attending Oto-laryngologist, New York Post-Graduate Hospital. Pp. 416; 146 engravings and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$5.50.

THIS treatise on otology is so concise, practical and clearly written that it can unreservedly be recommended to the undergraduate, the general practitioner and the postgraduate student. It is especially gratifying to this Reviewer to find the chapter on anatomy adorned with adequate and instructive illustrations, the absence of which has been glaringly conspicuous in many recent text books. The description of special functional examination of the hearing and equilibratory apparatus is explicit and instructive. General therapeutic measures in otology are treated in sufficient detail to guide the clinician in their practical application. The importance of allergy in diseases of the ear is outlined with clarity and excellent judgment.

A minimum of text achieves a clear presentation of symptomatology, differential diagnosis and the rationale of therapeutics while the surgical aspects of otology are fully considered and well illustrated. This volume very nearly approaches the ideal in a small textbook on otology.

H. S.

THE PRINCIPLES AND PRACTICE OF MEDICINE. Designed for the Use of Practitioners and Students of Medicine. Originally written by The Late SIR WILLIAM OSLER, BART., M.D., F.R.C.P., F.R.S., formerly Regius Professor of Medicine, Oxford University; Professor of Medicine, Johns Hopkins University, Baltimore, etc. Revised by HENRY A. CHRISTIAN, M.D., LL.D., S.D., F.R.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician in Chief, Peter Bent Brigham Hospital, Boston. (9th, 10th, 11th and 12th editions were revised by THOMAS McCRAE, M.D., F.R.C.P., Formerly Professor of Medicine, Jefferson Medical College, Philadelphia.) Pp. 1424; illustrated. Thirteenth Edition. New York: D. Appleton-Century Company, 1938. Price, \$9.00.

In this latest edition, this textbook, so long a favorite, has been conspicuously modernized by its new editor. The improved typography is larger, requiring more pages, but facilitating reading and with better selection of headings. New concepts are reflected in changes in arrangement of the diseases, notably of the infections. In the introductory remarks that open certain sections, aspects of pathologic physiology are discussed.

Etiology and treatment of important infections, notably lobar pneumonia and streptococcal diseases have been revised. The section on anemia has been in part rewritten. The section on Bright's disease, entirely rewritten, reflects the editor's preference for the simplest clinical classification and one that will appeal to many clinicians; the new paragraphs on uremia are not perhaps an improvement. The editor's method of presenting prognosis in heart disease in general and symptoms and treatment of cardiac decompensation in a special section is commendable.

This revision effectively prolongs the usefulness of a standard work.

J. A.

CHIRURGIE DER LUNGEN UND DES BRUSTFELLES. (Band 26 of Medizinische Praxis. Sammlung für Ärztliche Fortbildung, Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme and Prof. Dr. K. Warnekros.) By DR. ALFRED BRUNNER, Chirurg. Chefarzt am Kantonsspital St. Gallen; Früher Privatdozent für Chirurgie an der Universität München. Pp. 282; 112 illustrations. Dresden: Theodor Steinkopff, 1938. Price, Paper, Rm. 22.50; Bound, Rm. 24.00.

THIS little volume is one of a series of practical monographs on special subjects. The author hopes that it will bring together the many advances which have been made in the field of pulmonary surgery in the last few years. The surgery of the heart and mediastinum is not included. There are 10 chapters, a short bibliography, an author and a subject index. There are short chapters on lung abscess, gangrene, bronchiectasis and benign and malignant tumors. Nearly one-half of the monograph is concerned with a discussion of management of tuberculosis by collapse therapy. The management of acute and chronic empyema and tuberculous empyema is reviewed. While it should not be used as a textbook of thoracic surgery by the beginner, it will provide a bird's-eye view of the subject and be useful for reference. The majority of the references are continental and the Reviewer is surprised that no mention is made of the work of Graham or Churchill in the entire volume. Surely Graham's work in empyema and malignant disease, and Churchill's in bronchiectasis are more important than much which has been reviewed.

I. R.

UEBER DIE BEZIEHUNGEN DER QUALITÄT DES NAHRUNGSEIWEISSES ZUM ABLAUF DES BETRIEBSTOFFWECHELS. Heft 3. Schriftenreihe zur Schweizerischen Medizinischen Wochenschrift. By ADOLF BICKEL, Professor of Pathological Physiology in the Friedrich-Wilhelm University, Berlin. Pp. 100. Basel: Benno Schwabe & Co., 1938. Price, Fr. 10.

THIS short monograph contains a group of related papers, presenting the experimental data accumulated in the author's laboratory. As the title indicates, the purpose of the work was to study the effect of the quality of the food proteins upon "working metabolism" as distinguished from "structural metabolism." The latter term refers to processes associated with growth and regeneration, while the former term refers to metabolic processes, which may be measured by the daily drain of metabolites, C and N compounds, in the urine. The experimental work was largely upon rats, although data upon man is also presented. Many tables give figures for C and N outputs.

D. D.

MENINGIOMAS. Their Classification, Regional Behaviour, Life History, and Surgical End Results. By HARVEY CUSHING, M.D., Sometime Associate Professor of Surgery, Johns Hopkins University; Moseley Professor of Surgery, Harvard University, and Surgeon-in-chief, Peter Bent Brigham Hospital, Boston, etc. With the Collaboration of LOUISE EISENHARDT, M.D., Assistant Professor of Pathology, Yale University School of Medicine; Formerly Associate in Surgery, Peter Bent Brigham Hospital, Boston. Pp. 785; 685 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, \$15.00.

THIS work by two well-known investigators of neuro-pathological problems may be considered a sequel to the senior author's monograph on "Tumors of Nervous Acusticus," published in 1917. It is based upon a detailed analysis of 313 cases of meningiomas, all of them histologically verified. The meningiomas are broadly considered from the point of view of internist, neurologist, surgeon, and pathologist. Case histories contain-

ing all the necessary data are given, as well as operative procedures. The probable etiologic factors, the symptomatology, and the steps leading to diagnosis, the end results and pathologic aspects are clearly discussed. The many excellent illustrations include not only photographs of specimens but of patients as well. A well selected bibliography of over 500 titles is appended. The monograph is written in the lucid style that characterizes all the contributions with which Dr. Cushing's name is associated. Here is an altogether worth-while book, and a monument to the painstaking care and industry of an illustrious surgeon.

B. L.

ESSENTIALS OF OBSTETRICAL AND GYNECOLOGICAL PATHOLOGY. With Clinical Correlation. By MARION DOUGLASS, M.D., F.A.C.S., Assistant Professor of Gynecology, Western Reserve University, and ROBERT L. FAULKNER, M.D., Senior Clinical Instructor in Gynecology, Western Reserve University. Pp. 187; 148 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.75.

In this book are discussed briefly and from a clinical point of view the normal structures and the more important pathologic processes of the female sex organs. The book is accompanied by many good illustrations, most of them photographs illustrating gross and microscopic pathologic material. There are chapters on the vulva and vagina, the cervix, endometrium, the myomatous tumors of the uterus, endometriosis, the Fallopian tubes, ovary, and the pathologic conditions incident to gestation.

The book should prove of value to the graduate and undergraduate students of obstetrics and gynecology as a well written, clear, and brief text on the pathology of the female generative organs.

B. L.

THE CHEMISTRY OF THE AMINO ACIDS AND PROTEINS. Edited by CARL L. A. SCHMIDT, M.S., PH.D., Professor of Biochemistry, University of California. Pp. 1031; 259 illustrations and 144 tables. Springfield, Ill.: Charles C Thomas, 1938. Price, \$7.50.

As it is impossible to review a book of this magnitude in the small space allotted, the chapter headings with their authors will be sufficient to give an idea of the scope and thoroughness of this work.

Part I. Chemical Statics of Amino Acids and Proteins: Historical (C. L. A. Schmidt); The Constitution and Synthesis of the Amino Acids (M. S. Dunn); *a*, The Isolation of the Amino Acids from Proteins (H. O. Calvery); *b*, The Preparation of Amino Acids and Proteins (C. L. A. Schmidt); Methods of Analysis and Reactions of the Amino Acids and Proteins (H. O. Calvery); The Relation of the Amino Acids to Products of Biochemical Importance (C. L. A. Schmidt); Peptides, Peptidases and Diketopiperazines (J. P. Greenstein); The Chemical Constitution of the Proteins (R. J. Block); Certain Chemical and Physical Characteristics of the Proteins (15 sections) (M. L. Anson, Evert Gorter, A. A. Vander Dussen and L. Maaskant, D. M. Greenberg, C. L. A. Schmidt, J. T. Edsall); Optical Properties of Amino Acids and Proteins (D. M. Greenberg).

Part II. Chemical Dynamics of Amino Acid and Proteins. Amphoteric Properties of Amino Acid and Proteins (D. M. Hitchcock); Electrochemistry of Amino Acids and Proteins (C. L. A. Schmidt); Combination of Amino Acids and Proteins with Acids, Bases, Heavy Metals and Other Compounds (C. L. A. Schmidt); Membrane Equilibria (D. M. Greenberg); Some Thermodynamical Considerations of Amino Acids, Peptides, and Related Substances (H. Borsook and H. M. Huffman); Dipolar Ionic Structure and Solubility of Amino Acids, Peptides and Proteins (J. T.

Edsall); Relation of Proteins to Immunity (M. Heidelberger); The Rôle of Proteins in Nutrition (R. W. Jackson).

Although there are some errors and some of the more recent work is not included, this volume covers protein chemistry very completely. It is also very well edited as there is practically no repetition of material in spite of its being written by a number of authors. J. J.

DER ZYKLUS DER FRAU. Reform Des Ehelebens. By DR. JULES SAMUELS, Chirurg-Frauenarzt, Leiter der Einrichtung für Kurzwellentherapie, Amsterdam. Pp. 175; 43 illustrations (some in colors). Haag: G. Naeff, 1938. Price not given.

WRITTEN for lay consumption, this book offers a new method of determining the time of ovulation, presence of pregnancy and the problems of menstruation with both normal and abnormal women.

The proposed simple examination by which these conditions may be determined is made possible by the use of a new instrument, the "Cycloscope." This consists of a spectroscope and a powerful lamp mounted on a stand with an examining platform upon which the patient's hand is to be placed. This test is made by examining the delicate tissue between the thumb and forefinger with relation to the spectroscopic changes in the oxyhemoglobin content of the blood as it passes this point. The reduction time figured by changes in the spectroscopic analysis of the blood viewed through the instrument is believed to bear a very definite relation to the hormone content of the blood of the woman.

The book is illustrated with colored plates indicating changes in the spectroscopic readings. Cyclograms show the relationship of menstruation and other objective changes to the recorded reduction times. Samuels demonstrates by such graphs that more than one ovulation per cycle is likely, and frequently happens in many women, and seeks thereby to disprove the theory of Knaus-Ogino. He states that the first and second ovulations are usually from 5 to 7 days apart. P. W.

MANUAL OF VETERINARY BACTERIOLOGY. By RAYMOND A. KELSER, D.V.M., A.M., Ph.D., Lieut. Colonel, Veterinary Corps, United States Army; Chief, Veterinary Division, Surgeon General's Office, War Department, Washington, D. C., etc. Pp. 640; 93 illustrations and 11 tables. Third edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1938. Price, \$6.00.

THE third revised edition is 90 pages longer than the previous one and contains additional valuable information in most of its parts. Advancements in the field of immunology have been taken into account and the author presents a fuller discussion of virulence of bacteria and of dissociation.

Bergey's classification of bacteria is essentially adhered to, including the changes of the 1934 edition. In the section dealing with pathogenic organisms new information is incorporated, namely, the bacteriology of *vibrio jejuni*, *hemophilus influenzae* (suus), *hemophilus canis*, *corynebacterium equi* and a more detailed discussion of the streptococcus group. The section on pathogenic fungi is enriched by the description of *trypanosoma cruzi*, the cause of Chagas' disease. More recently established virus diseases as swine influenza, fowl tumors, rabbit fibroma, rabbit papilloma and equine infectious abortion are included.

The book contains very useful information for the student and laboratory worker in animal bacteriology and the author is to be congratulated for bringing it up to date in the present edition. E. S.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. IX. Mumps to Pneumothorax, Spontaneous. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, G. GREY TURNER, JAMES YOUNG, SIR LEONARD ROGERS, F.M.R. WALSHE. Pp. 805; 117 illustrations and 10 plates (1 in color). London: Butterworth & Co. Publishers, Ltd., 1938. Price, \$12.00.

As usual in this Encyclopedia, a number of well-known names appear in the list of authors. Among the subjects treated at greater length are Nephritis and Nephrosis, Neuritis, Diseases of the Oesophagus, Ovary, Parathyroid, Placenta, Peptic Ulcer, Plague, and Lobar Pneumonia. Even these subjects, however, and even in such an extensive encyclopedia as this one is, cannot be expected to receive the kind of treatment that they would receive in a monograph, or System of Medicine. E. K.

CARBON MONOXIDE ASPHYXIA. By CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology and Dean, School of Public Health, Harvard University. Pp. 276; 40 illustrations, and 21 tables. London: Oxford University Press, 1938. Price, \$4.50.

"This book is written primarily for men who have practical concern with the problems of carbon monoxide asphyxia" says the author in his preface. It will serve this purpose admirably for it is clearly written, and most of the points made are so expressed as to be intelligible to those with little scientific background. In spite of this commendable simplicity, it gives an excellent account of the subject from the professional viewpoint and there will be few physiologists who will not find it a valuable source of information. The whole account is well illustrated by detailed reports of individual reactions to carbon monoxide poisoning and includes some of the graphic descriptions given by the late Professor J. S. Haldane of his own historical experiments. An interesting historical account is also given of the various means of artificial respiration. The bibliography contains 335 references with titles. There can be little question but that this book will prove extremely useful alike to laymen, clinicians and physiologists.

H. B.

PRACTICAL PROCEDURES. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. With a Preface by SIR DAVID WILKIE, O.B.E., M.D., M.Ch., F.R.C.S., F.A.C.S., F.R.S.E. Pp. 293; 66 illustrations. London: Eyre and Spottiswoode (Publishers), Ltd., 1938. Price, 10s. 6d.

THIS is a handbook intended to serve the general practitioner as a practical guide to clinical procedures. Eighteen authors have contributed chapters on such topics as plaster-of-Paris technique; administration of fluids; indications and technique for blood transfusions; pleural aspiration; the use of two- and three-way syringes; catheterization; circumcision in children; minor surgical affections of the skin; local anesthesia; lumbar puncture in general practice; syringing the ear. The advantage of such a book is that it includes material which would otherwise have to be looked for in many textbooks. The subject matter is concise and practical, and the illustrations are adequate.

R. K.

BOOK REVIEWS AND NOTICES

THE NEW-BORN INFANT. A Manual of Obstetrical Pediatrics. By EMERSON L. STONE, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale University; Attending Obstetrician and Gynecologist to the New Haven Hospital. Pp. 291. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$3.00.

The second edition of this little treatise on the care of newly born infants shows an enlargement of approximately 100 pages. It is in consequence up to date in most respects and more valuable than the first to the practitioner.

The author reiterates his belief that the "new-born period" is neglected alike by obstetrician and pediatrician. It is the opinion of this Reviewer that progress in this field has come through the pediatric study of the new-born. In most good hospitals these cases are cared for by pediatricians and have been for many years. In consequence of the authors' obstetrical training those sections of the book which deal with the immediate or emergency case of the infant and with the accidents incident to delivery are handled most capably. Such matters as resuscitation of the infant and, intracranial hemorrhage are completely and excellently covered.

One feels that the introduction of tables of data, more references, and a few well chosen illustrations would enhance the value of the book. In the main, it serves as an introduction to the subject rather than as a complete treatise and is of great value to the beginning student.

E. T., Jr.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. XI. Tagung. Zu Bad Nauheim vom 26.-27. März 1938. Herausgegeben von Prof. Dr. E. B. Koch, Bad Nauheim. Pp. 430; illustrated. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 11.25.

The *Hauptthema* of this session was Circulatory Collapse to which more than 20 articles in this volume are devoted. Burns, hemorrhage, surgery, histamine, child birth, lung emboli, all are discussed and various opinions maintained. There are also 16 papers on miscellaneous subjects. One does not recognize many familiar names among the authors; the long Autoren-Register is a useful list referring to all authors mentioned in the text.

E. K.

DRUG ADDICTS ARE HUMAN BEINGS. The Story of our Billion-Dollar Drug Racket, How We Created It and How We Can Wipe It Out. By HENRY SMITH WILLIAMS, M.D., B.Sc., LL.D. Pp. 273; illustrated. Washington, D. C.: Shaw Publishing Company, 1938. Price, \$2.50.

In 1914, the Harrison Narcotics Law was enacted, the intent of which was to have physicians sole distributors of narcotic drugs; since then, the Supreme Court has ruled that addiction is a disease; furthermore, in the review of a narcotic case in 1935, the Supreme Court declared the Federal Government has no control over the practice of a profession. Nevertheless, the Narcotic Code has often denied addicts the right of procuring narcotic preparations from physicians. By reason of this illegal ruling, many addicts have had recourse to drug peddlers, to whom they sometimes paid an exorbitant price for a greatly adulterated product. It is estimated we have at least 500,000 addicts, three-fourths of whom are said to be engaged in gainful pursuits. In Los Angeles, a Narcotic Clinic was established for afflicted addicts. And, "though monumentally successful during the three years of its operation, fell before the organized attack of the Federal coadjutors of the billion-dollar racket," despite their illegal and unconstitutional actions. Approximately 25,000 physicians have been prosecuted, with fines as high as \$10,000 and sentences as much as ten

years, "after having committed no crime!" It is said that the remedy for "Our Billion-Dollar Racket" is not a new law, but recognition of the rulings of the Supreme Court; by the lower courts. Justice Roberts has stated: "Federal law cannot regulate the practice of a profession." However, present indications are that we shall have Federal control. One wonders at the rapid spread of the narcotic vice, with so much of peddlers' supply an inferior product, at extortion prices. N. Y.

MODERN ANÆSTHETIC PRACTICE. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, Bt. G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. Pp. 231; illustrated. London: Eyre & Spottiswoode (Publishers) Ltd.; 1938. Price 10s. 6d.

THIS book is not a contribution to the scientific advancement of anesthesia and in some parts falls distinctly short of modern anesthetic practice as taught by the best anesthetists in this country. The chapter that deals with the theoretical aspects consists of many statements from the literature without due regard to their source. Emphasis is placed on the technical methods of anesthesia in England and this is quite properly stressed in this book. However, even in a practical treatise, the fundamental physiological principles should be given more attention than they have been in most of the several chapters of this book. It is therefore not suitable for a textbook and only certain chapters are worthy for use as references. No doubt it fills the purpose for which it was written, namely as an aid to the general practitioner in England; but because of the differences in anesthetic training it does not have the same value in the United States. L. F.

SUBACUTE AND CHRONIC PERICARDIAL AND MYOCARDIAL LESIONS DUE TO NON-PENETRATING TRAUMATIC INJURIES. A Clinical Study. By ERIK WARBURG, M.D. With a Short Biography of Oluf Borch (Olaus Borrichius) by TORBEN GEILL, M.D. Pp. 147; 18 illustrations. Copenhagen: Levin & Munksgaard, 1938. Price, Kr. 14.00. (London: Humphrey Milford; Oxford University Press, Price, 12s. 6d.)

DESIRING more detailed knowledge about cardiac disease resulting from non-penetrating trauma, the author has collected from the literature and analyzed 184 examples of pericardial and myocardial lesions from this cause, and added 12 "new" cases, of which he gives detailed records. He found disorders ranging from transient electrocardiographic changes and arrhythmias to rupture and sudden death and notes that many developed congestive heart failure. He believes that it is a much commoner cause of heart disease than is generally suspected. The 2 first cases reported—by Olaus Borrichius and Stephen Blankaard—are reproduced in English and in facsimile together, with a biography of Borrichius. E. K.

PRACTICAL MICROBIOLOGY AND PUBLIC HEALTH. For Students of Medicine, Public Health, and General Bacteriology. By WILLIAM BARNARD SHARP, S.M., M.D., PH.D., Professor of Bacteriology and Preventive Medicine in the Medical Department of the University of Texas; Visiting Bacteriologist of John Sealy Hospital, Galveston, etc. Pp. 492; 125 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.50.

THIS work is an effort to include in one "laboratory" manual all of the subjects covered in a course of training for public health workers. The book embraces as laboratory exercises general bacteriology, vehicles of infection, clinical bacteriology and mycology, immunology and animal para-

sitology. In addition are included directions for field surveys and the handling of office problems of administration.

While as a manual of directions for use of students taking a course covering the included subjects it would no doubt be very helpful, the Reviewer doubts the wisdom of attempting to cover so much ground in one manual. For the student it would be better to have the subject matter split up into three or more smaller manuals. To keep a laboratory manual up to date and not have it too static, it is better to issue it as loose leafed mimeographed material easily revisable from year to year.

In no way can this book be regarded as a text book. Even as a manual it seems to the Reviewer to be inadequate, as the effort to simplify and condense has resulted in inadequacy and incompleteness of directions, lack of clear explanations of procedures and results, and in the omission of various newer methods.
H. S.

SPINAL ANESTHESIA. By LOUIS H. MAXSON, A.B., M.D., Practising Specialist in Anesthetics; former Chief Anesthetist, Harborview (King County) Hospital, Seattle, Wash. Foreword by W. WAYNE BABCOCK, M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. Pp. 409; 69 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, \$6.50.

THE author has reviewed the subject of spinal anesthesia from the physical, anatomic and physiologic viewpoint according to the literature to date. He has added to this his personal experience and discussed many of the points over which controversy still exists.

The physical aspects of spinal anesthesia are well presented. While the claims for this type of anesthesia are, as the author states, more conservative than in some texts of the past, they are those of an enthusiast for spinal anesthesia. The book has a subject index and complete bibliography. It is a good text for reference purposes and will prove helpful to those who have not had the opportunity to follow the literature on the subject.
I. T.

NEW BOOKS.

Trauma and Internal Disease. A Basis for Medical and Legal Evaluation of the Etiology, Pathology, Clinical Processes, Following Injury. By FRANK W. SPICER, A.B., M.D., F.A.C.P. Pp. 593; 43 illustrations. Philadelphia: J. B. Lippincott Company, 1939. Price, \$7.00.

Textbook of Neuro-anatomy and the Sense Organs. By O. LARSELL, Ph.D., Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 343; 232 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, \$6.00.

Out of the Running. By G. GERTRUDE HOOPES. With a Foreword by EDGAR A. DOLL, Ph.D., Director of the Department of Research, The Training School at Vineland, New Jersey, and with Clinical Notes by WINTHROP M. PHELPS, M.D., Director of the Children's Rehabilitation Institute, Inc., Baltimore. Pp. 158; illustrated. Springfield, Ill.: Charles C Thomas, 1939. Price, \$2.00.

Life's Beginning on the Earth. By R. BEUTNER, M.D., Ph.D., Professor of Pharmacology at the Hahnemann Medical College and Hospital of Philadelphia. Pp. 222; 80 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, \$3.00.

Medizin und Kultur. Gesammelte Aufsätze. By PAUL DIEPGEN. Zu seinem 60. Geburtstag am 24. November, 1938. Herausgegeben von W. ARLETT, E. HEISCHKE, J. SCHUSTER. Pp. 309. Stuttgart: Georg Thieme Verlag, 1938. Price, Paper, Rm. 21, Bound, Rm. 22.80.

Surgical Pathology of the Diseases of the Mouth and Jaws. By ARTHUR E. HERTZLER, M.D., Surgeon to the Agnes Hertzler Memorial Hospital, Halstead, Kansas; Professor of Surgery, University of Kansas. Pp. 248; 206 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, \$5.00.

Medicine in Modern Society. By DAVID RIESMAN. Pp. 226; Princeton: Princeton University Press, 1938. Price, \$2.50.

The Medical Clinics of North America, Vol. 23, No. 1 (Chicago Number, January, 1939). Pp. 271; 23 illustrations. Philadelphia: W. B. Saunders Company, 1939.

The Symposium on the Gall Bladder—10 contributors—is chiefly devoted to the newer aspects of diagnosis and treatment of this clinically important organ. The 15 other papers by Chicago doctors cover a wide range such as Hamburger on Bradycardia, Coulter on Diathermy, Bernstein on Allergy, and W. O. Thompson on the Hypothyroid State.

The Medical Press and Circular, 1839–1939. A Hundred Years in the Life of a Medical Journal. By ROBERT J. ROWLETTE, M.D., F.R.C.P.I. Pp. 127; illustrated. London: The Medical Press and Circular, 1939. (No price given.)

The Medical Press and Circular, founded in Dublin by Dr. Arthur Jacob in January, 1839, under the title of the Dublin Medical Press, celebrates its Centenary with a history of the journal and its development, together with an interesting account of the medical history of the times. In 1866 it combined with the Medical Circular, a London periodical founded in 1852. This journal had an eventful career: its more or less continuous warfare with Wakley of the Lancet and its long series of illustrated biographies were conspicuous. The combined journal has continued to occupy a useful place in English medical literature. The volume is artistically produced; its 10 plates include portraits of the early editors and reproductions of the various title pages.

Cronología, diferenciación, matrícula y distribución geográfica de las sociedades de ciencias médicas. By ENRIQUE SPARN, Secretario de la Academia Nacional de Ciencias. Pp. 153; illustrated. Cordoba: Universidad Nacional de Corboda, 1938. (No price given.)

In the Preface it is stated that this is the only monograph of its kind in print. In five parts cover: 1, a list of societies in order of their date of foundation; 2, their general nature; 3, their size; 4, their geographical distribution; and 5, the largest section, their division into 28 different classes. Though far from being exhaustive, this should be a useful reference book for those wanting information on the subject.

The Proceedings of The Charaka Club, Vol. IX. Pp. 204; illustrated. New York: RICHARD R. SMITH for the Charaka Club, 1938.

Principles of Hematology. By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division of the Cleveland Clinic; Formerly Professor of Experimental Medicine in the University of Kansas School of Medicine, Kansas City, Kansas. Pp. 348; 155 illustrations and 1 colored plate. Philadelphia: Lea & Febiger, 1939. Price, \$4.50.

Del Carcinoma Primitivo Broncopulmonar. By NICETO S. LÓIZAGA, Profesor adjunto de Patología Médica, Docente libre de Clínica de Enfermedades Infecciosas de la Facultad de Ciencias Médicas de Buenos Aires. Pp. 221; illustrated. Buenos Aires: Librería y Editorial "El Ateneo," 1938.

Based on 46 original cases of primary carcinoma of lung, and reports from the literature, the authors consider the subject from the point of incidence, etiology and pathogenesis, pathology, symptoms, diagnosis, prognosis and treatment.

A Manual of Fractures and Dislocations. By BARBARA BARTLETT STIMSON, A.B., M.D., MED. SC.D., F.A.C.S., Associate in Surgery in the College of Physicians and Surgeons, Columbia University, New York City; Assistant Attending Surgeon to the Presbyterian Hospital, New York City. Pp. 214; 95 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$2.75.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 10. Poisons Legislation to Rosacea. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic; Cambridge; Sometime President of the Royal College of Physicians of London, with the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. WALSH, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 731; 79 illustrations and 11 plates (4 in color). London: Butterworth & Co. (Publishers), Ltd., 1938. Price, \$12.00 per volume.

The present volume covers from Poisons Legislation through Rosacea, the most extensive articles being, as one might expect, on Pregnancy and the Psychoses. Perusal, though admittedly brief, indicates that the high standard of previous volumes has been maintained.

NEW EDITIONS.

Immunity Principles and Application in Medicine and Public Health. An Exposition of the Biological Phenomena of Infection and Recovery of the Animal Body from Infectious Disease, with Consideration of the Application of the Principles of Immunity to Diagnosis, Treatment, and Prophylaxis and Their Usefulness in the Control of Epidemics. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunology, Harvard Medical School, JOHN F. ENDERS, Ph.D., Assistant Professor of Bacteriology and Immunology, Harvard Medical School, and LEROY D. FOTHERGILL, M.D., Assistant Professor of Bacteriology and Immunology and Associate in Pediatrics, Harvard Medical School. Pp. 801. Fifth Edition of "Resistance to Infectious Diseases." New York: The Macmillan Company, 1939. Price, \$6.50.

Fundamentals of Experimental Pharmacology. By TORALD H. SOLLMANN, M.D., Sc.D., Professor of Pharmacology and Materia Medica, and Dean of the School of Medicine, Western Reserve University, Cleveland, etc., and PAUL J. HANZLIK, A.M., M.D., Professor of Pharmacology, Stanford University School of Medicine, San Francisco, etc. Pp. 307; 36 illustrations. Second Edition. San Francisco: J. W. Stacey, Inc., 1939. Price, \$4.25.

Infections of the Hand. A Guide to the Surgical Treatment of Acute and Chronic Suppurative Processes in the Fingers, Hand and Forearm. By ALLEN B. KANAHEL, M.D., Sc.D., Late Professor of Surgery, Northwestern University Medical School, Chicago; Attending Surgeon, Wesley Memorial and Passavant Memorial Hospitals, Chicago. Pp. 503; 229 illustrations (many in color) and 1 colored plate. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$6.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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THE BOVINE TUBERCLE BACILLUS IN HUMAN TUBERCULOSIS.

ROBERT KOCH, at the International Congress on Tuberculosis in London in 1901, grudgingly acknowledged the existence of the bovine type of tubercle bacillus, but regarded it as of no real significance in human infection. He modified this extreme view in Washington, in 1908, but since pulmonary tuberculosis constitutes by far the greatest proportion of tuberculous infection in man, and believing it was invariably caused by the human type, he still maintained that bovine tuberculosis was of slight significance in the human disease.

The purpose of this review is to indicate the increasing evidence for the importance of the bovine tubercle bacillus not only in extrapulmonary tuberculosis, but also its frequency in tuberculosis of the lung which was until recently regarded as almost non-existent.

In the general problem of the control of tuberculosis the infections with the bovine type of bacillus are fully preventable. They depend upon the eradication of the disease in cattle or the control of the milk supply by pasteurization. In those countries where milk is boiled before consumption bovine infection in man is relatively infrequent.

Isolation. The inoculation of the guinea pig has been until recently practically the only method used for the primary isolation of mammalian tubercle bacilli. It is important to realize that these bacteria are not always easy to grow, particularly when dealing with the bovine type from human sources, and the growing tendency to substitute cultural for animal inoculation methods must unquestionably result in failure to isolate bovine strains in certain instances. Animal inoculation and cultural methods were used: by Griffith^{49c} in studying strains from skin lesions; by Gosling and Montanus⁴⁶ in a study of 34 specimens of cerebrospinal fluid in suspected tuberculous meningitis, and tubercle bacilli were obtained 25 times in culture; by Griffith^{49l} who reserved the animal test for material showing a paucity of organisms, or in those secondarily infected; by Ledermann^{69a} who reported better results by the use of cultural methods; by Lange^{66b} in his studies of bovine phthisis

(tuberculosis of lung in man caused by the bovine type); by Stadnichenko and Sweany¹²² in a study of pulmonary tuberculosis. They isolated human tubercle bacilli from 69 cases out of 200 studied; of these, 33 were positive on both culture and guinea pig inoculation; 33 in guinea pig inoculation, and negative in culture; and 3 were positive in culture but negative in guinea pig inoculation; by Feldman⁴¹ who found in 27 specimens from various human sources 24 positive on guinea pig inoculation while 23 were positive in culture; and in a study of 19 specimens of bovine material (from bovine sources) 18 strains were recovered on guinea pig inoculation and 16 by culture; by Saenz, Le Mée and Costil¹¹⁴ who stated that cultural methods suffice for material in which 4 tubercle bacilli can be seen in each high power field; by Lester⁷¹ who reserved guinea pig inoculation for all material from children under 5 years of age, the age group in which the highest incidence of bovine infection is known to occur; by Mündel and Stempel⁸³ in all cases of suspected bovine tuberculosis; by Blacklock and Griffin¹³ in a comprehensive study of tuberculous meningitis in children, and they emphasized that cultural methods were positive only in 50% of the bovine strains recovered from the cerebrospinal fluid; by Piasecka-Zeyland¹⁰¹ in his general survey studies in Poland; and Lange^{66c} in the isolation of the tubercle bacillus from the sputum in a survey study of bovine phthisis, while Ruys¹¹¹ preferred guinea pig inoculation to cultural methods in survey work upon the incidence of bovine tuberculosis in Holland.

Jensen and Frimodt-Møller⁶⁰ have since 1934 used cultural methods exclusively and were successful in culturing many bovine strains. Rocher and Laporte¹⁰⁸ and Saenz^{112b} used cultural methods extensively but not solely. Green⁴⁸ in routine work, in an analysis of results obtained in a study of 1306 specimens by means of culture and guinea pig inoculation, concluded that cultural methods are practicable, but that animal inoculation gave as a rule a higher number of positives. No mention is made of the types of tubercle bacilli recovered.

The method of Negre, Valtis, Van Deines and Beerens,⁹⁰ which according to the authors permits the isolation of the tubercle bacillus through guinea pig inoculation in some cases where the ordinary inoculation is negative, consists in treating the inoculated animals with an acetone extract of the Koch bacillus. Strains of acid-fast bacilli of extraordinary biologic qualities were thus recovered which are designated as probably "intermediates." Valtis and van Deins¹³¹ believed that by this method filtrable forms of tubercle bacilli are developed, and that they could differentiate these filtrable forms of tubercle bacilli from the acid-fast forms occasionally found in the glands of normal guinea pigs (found in 9 uninoculated animals). This work has not been confirmed, and will need a great deal of controlled work before it can be accepted as valid.

Cultivation. In growing tubercle bacilli, particularly from small plantings, special conditions must be maintained and special media used. In cultivating the human type glycerin, first used by Nocard and Roux,⁹¹ should be added to media containing potato, egg or mixtures of these. No attempt will be made to even list the numerous media and modifications which have been reported. The glycerin potato cylinder developed by Pawlowsky⁹⁶ at the Pasteur Institute has been

extensively used and the chief modification is that of Corper and Uyei²⁴ who used crystal violet solutions to prevent overgrowth by contaminants.

Dorset³⁴ used the first and simplest of the egg media. Lubenau⁷⁷ modified it by adding glycerinated extract broth, Petroff¹⁰⁰ by gentian violet and veal infusion, and Petragnani⁹⁹ added potato, peptone, milk and malachite green. The latter has been highly recommended by almost all who have used it. Loewenstein⁷⁶ substituted a synthetic medium containing asparagin for the peptone and added Congo red. This medium also has given excellent results. Herrold⁵⁵ added unheated egg yolk to a plain and a glycerinated agar. Jensen^{59b} slightly modified Loewenstein's medium and reduced the amount of glycerin from 5 to 0.75%. This is the medium of choice among the Danish workers. Schwabacher¹¹⁸ in a comparative study of many of the above media found a simple heated egg medium (3 parts yolk of egg to 1 part saline with or without glycerin) to be best suited for growing the tubercle bacilli. In 1938, Boissevain and Schultz¹⁵ discovered that the growth factor in the egg yolk is an alcohol soluble lipoid and this is also to be found in the liver and spleen of guinea pigs and rats.

It would appear that good results can be obtained by a variety of media and in the hands of the experienced worker the simplest medium is as satisfactory as the most complicated.

Differentiation. Differentiation of bovine human tubercle bacilli depends upon: (1) The slow growth of colorless moist colonies of the bovine (dysonic) as contrasted with the more actively growing, dry pigmented colonies of the human (eugonic) (the latter being definitely enhanced by the use of glycerin which tends to inhibit the bovine type); (2) the high degree of pathogenicity of the bovine, the low or total lack of pathogenicity of the human for the rabbit. Both, of course, are highly pathogenic for the guinea pig.

Incidence. The total incidence of bovine tubercle bacilli in human tuberculous infection is approximately 10%. This is based upon the analysis of about 18,000 strains reported from various parts of the world. The geographic distribution of these bovine infections is extremely interesting. The greatest number occurred in Great Britain (Scotland having the highest figure in all varieties of infection) (Table 1), Denmark (Table 2) coming next. These two countries, it should be noted, have done by far the greatest amount of research on this problem. Germany is next in the list, but since few recent statistics are available no conclusions are justifiable. The figures for the remaining European countries are fragmentary and are of academic rather than scientific value. The statistics for the United States are based chiefly on the reports of Park and Krumwiede,⁹⁴ Aronson and Whitney,⁶ van Es,³⁹ and Chang.²² The surprising results given by Chang probably do not represent present-day conditions. However, vital statistics from the United States show that a direct parallelism exists between the eradication of tuberculosis in cows and the striking reduction in mortality from extrapulmonary forms of tuberculosis.

Table 3 shows the reported incidence in various countries, excepting Britain and Denmark. In determining the number of cases of bovine infection in various countries it must be realized that the amount and the quality of the bacteriologic diagnoses vary within very wide limits. The figures presented are, therefore, at best nothing more than an

approximation of the total number of cases of bovine infection in man, but the more reliable British and Danish results are sufficient to show clearly the importance of the problem.

There are a number of interesting phases in the bacteriologic analyses of the materials which will be considered under separate headings.

Mixed and Double Infections. A mixed infection is one in which both types of tubercle bacilli are present in the same site. The discovery of such infections was made possible by the inoculation of rabbits and the observation of the types of growth in cultures. Differentiation by the characters of the colonies is the safer method since it eliminates the possible spontaneous infection of the inoculated animals. There have been reported 25 such cases. Kossel⁶⁴ reported such isolations from the sputum of a case of pulmonary tuberculosis, Lindemann⁷⁴ a similar case, Lange^{66a} the same, Daddi and di Natale³⁰ 2 such cases, Valtis, Paiseau and van Deinse¹³² 1 from the gastric washings of an infant, and Ruys^{111a} 2 cases from similar material. Jensen^{59c} reported 6 cases of mixed infection from Denmark, all these patients were suffering from ulcerative pulmonary tuberculosis. In 5 of the 6 cases the organisms from the sputum showed two distinct types of colony. In the sixth case, bovine tubercle bacilli only were recovered from the sputum; but at autopsy human and bovine bacilli were isolated from the lungs, liver, spleen, and mesenteric glands while a bronchial gland yielded human bacilli only.

In Great Britain 9 cases of mixed infections are reported among some 6000 cases of tuberculosis investigated bacteriologically. The cases recorded are as follows: 1, Griffith,^{49a} a child dead of generalized tuberculosis. Human tubercle bacilli were isolated from mesenteric glands, lungs and meninges. Mixed human and bovine tubercle bacilli were recovered from a bronchial gland. 2, Griffith,^{49a} a youth, 18 years, dead of ulcerative phthisis. A calcareous mesenteric gland yielded human and bovine tubercle bacilli. 3, Griffith,^{49a} a man, aged 70 years, died of pneumonia. Human tubercle bacilli were recovered from a mesenteric gland. Mixed human and bovine bacilli were recovered from a retroperitoneal gland. 4, Griffith^{49a} reported the case of a child aged 5 years who died of tuberculous meningitis. The strain from the meninges was lost. Bovine and human tubercle bacilli were recovered from a bronchial gland. 5, Cumming, Foster, Girdwood and Griffith²⁸ reported the case of a mixed infection in a woman of 24 years. Bovine tubercle bacilli were recovered from the sputum on several occasions, later only human bacilli. Human and bovine bacilli were recovered at autopsy from lung, bronchial and calcareous mesenteric glands. 6, In a boy of 7 years with pulmonary tuberculosis Munro^{84b} reported mixed human and bovine tubercle bacilli from the sputum. 7, Munro^{84b}, and 8, Griffith and Munro,^{51a} from 2 children under 5 years of age who died of generalized tuberculosis, obtained a mixed culture from tracheobronchial glands. 9, Griffith^{49a} reported a case of mixed infection in a girl of 18 years, who died of tuberculous meningitis. A bovine strain was recovered from the meninges while mixed human and bovine bacilli were isolated from the lung. In addition, de Besche¹¹ reported a case from a mesenteric gland in an infant, and Goeters⁴⁴ recovered at autopsy human and bovine bacilli from the lung, and a pure culture of bovine bacilli from a mesenteric gland.

Double infections are those in which one or other type of bacillus is found in separate lesions. The number reported is 12. Kossel, Weber and Heuss^{65b} reported the first case of double infection in man. They recovered at autopsy bovine tubercle bacilli from a mesenteric gland, and human bacilli from a bronchial gland. Weber and Taute¹³⁸ reported a case in a child of 5 years in which bovine bacilli were recovered from the mesenteric glands and the human type from the spleen. Park and Krumwiede^{94a} in an infant obtained human bacilli from the mesenteric glands and bovine tubercle bacilli from cerebrospinal fluid. Steffenhagen¹²³ isolated from an infant bovine tubercle bacilli from the bronchial glands, and human bacilli from the mesenteric glands. Rothe and Bierrotte¹¹⁰ obtained bovine bacilli from lupus of the nose, and human bacilli from lupus of the buttocks. Ungermann¹³⁰ reported human tubercle bacilli from the knee joint, and only on one occasion bovine bacilli from the sputum, in a man of 37. Lewis⁷³ from a butcher of 52 years found a bovine strain from a lupus lesion and human tubercle bacilli from the sputum. Blacklock¹² reported 2 cases of double infection. 1, A boy of 2 years with tuberculous meningitis who was born in the country, but had lived in the same house with a grandmother and aunt who suffered from pulmonary tuberculosis. From the tracheobronchial glands human tubercle bacilli were isolated. From the mesenteric glands a bovine strain was obtained. 2, From a child at autopsy human tubercle bacilli were recovered from the tracheobronchial glands and human and bovine bacilli from the mesenteric glands. Stürz¹²⁶ in a case of tuberculosis of the skin recovered human and bovine bacilli from two different areas. Saenz, Coste and Costil¹¹³ in a man of 56 with tuberculosis of the skin and pulmonary tuberculosis, in whom the skin lesion had been present since 8 years of age, grew from the skin a bovine strain and from the sputum a human strain. Lange^{66d} reported a case of lupus from which he isolated bovine tubercle bacilli from a skin lesion over the right knee joint, and human tubercle bacilli from the lesion of the right upper arm.

It is surprising, considering the frequency with which bovine tubercle bacilli are found in man, that mixed or double infections occur so rarely. In attempting an explanation for this it is suggested by Griffith^{49a} that human and bovine tubercle bacilli rarely enter the body together. When they do, they may set up independent lesions at the different portals of entry, or they may colonize in the same gland or organ. The more frequent occurrence must be the entrance of one type at a time. If some immunity has developed as a result of the first infection the bacilli of the second infection are probably prevented from multiplying and eventually die out. On the other hand, if general resistance is not sufficiently enhanced by the first infection, the second will find conditions favorable and the bacilli are able to spread locally and into neighboring glands. It is noteworthy in connection with the cases of mixed infection recorded that the organisms were recovered from the mesenteric glands, bronchial glands and lung. There is no record of authentic occurrence of mixed infection in lesions distant from the portal of entry.

Atypical Strain. Griffith and his collaborators in Great Britain, Lange and Neufeld in Germany, Park and Krumwiede in the United States, maintained that the type is fixed. They regarded atypical

forms of tubercle bacilli as temporary variants of one or the other of the two fixed types.

Atypical strains differ either culturally or in pathogenicity from the standard, as laid down by the British Royal Commission^{16,17} and rather generally accepted. The following atypical strains have been reported in the literature:

1. *Eugonic Bovine Strains*. These are those strains which grow more readily than the standard bovine strains at the time of isolation but which possess the characteristic high pathogenicity for the rabbit. There have been only three such strains reported, two by Griffith^{49d} and one by Jensen and Frimodt-Møller.^{60a}

2. *Dysgonic Human Strains*. These are like the bovine tubercle bacillus in *initial* cultures but show a low pathogenicity for the rabbit and may be restored to the normal human type of growth by repeated subculture on artificial culture media. The British workers have reported 37 such strains as follows: Eastwood, Griffith and Griffith³⁷ isolated a strain from a case of generalized tuberculosis; Griffith,^{49b} 2 strains and later^{49c} 2 strains from the sputum; Eastwood and Griffith,³⁶ 10 strains from bone and joint tuberculosis; Griffith,^{49f} 5 from bone and joint tuberculosis; ^{49g}, 1 from the cervical glands; ^{49h}, 1 from the sputum; ⁴⁹ⁱ, 2 from bone and joint tuberculosis; ^{49j}, 1 from the meninges, and in 1932^{49o} 1 from the meninges. Griffith and Munro^{51b} reported 3 strains isolated from the sputum; Band, Alston, Griffith and Munro,¹⁰ 1 from the kidney; Griffith and Smith,⁵² 5 from the sputum; and Griffith and Menton,⁵⁰ 2 strains, 1 from the sputum and the second from a case of bone and joint tuberculosis. In addition, the other atypical human strains reported are as follows: Aronson and Whitney,⁶ 5 strains recovered at autopsy; Daddi,²⁹ 39 from the sputum; Daddi and di Natale,³⁰ 5 more such strains. Jensen and Frimodt-Møller^{60a} reported 3 such strains which they suggest might belong to the "intermediate" type (*q.v.*), and Cellina²¹ 2 isolated from the kidney at operation. The work of Daddi²⁹ and of Daddi and di Natale³⁰ differs from all others in recovering such a high incidence of atypical strains, in that the 44 strains discovered were from only 542 strains isolated. The 37 strains reported by Griffith and his associates are from a total of about 6000 strains studied. The criteria used by the Italian workers would appear to be different from those of others.

3. *Attenuated Human Strains*. These are culturally typical but the pathogenicity is greatly reduced for the guinea pig. Only 3 have been reported if we except those recovered from skin lesions. These latter will be discussed later. Griffith recovered an attenuated human strain of tubercle bacilli from the cervical glands in 1917,^{49g} another attenuated human strain in 1932^{49c} and Jensen and Frimodt-Møller^{60c} reported 1 such strain.

4. *Attenuated Bovine Strains*. These are those in which pathogenicity is reduced for the rabbit and the guinea pig, but the cultural characters are typically dysgonic. There are 26 reported, not counting those isolated from skin lesions (*q.v.*). Duval³⁵ recovered a strain from the cervical glands; Weber and Steffenhagen,¹³⁷ 1 from a case of bone and joint tuberculosis; Griffith,^{49h} 1 at autopsy, from the bronchial glands of an infant; Munro and Cumming,⁵³ 2 from bone and joint tuberculosis;

Rabinowitsch-Kempner,^{105b} 1 from the sputum in pulmonary tuberculosis; Griffith,⁴⁹ⁱ 2 from bone and joint tuberculosis, and in 1932,^{49p} 3 strains from various sources. Price^{103b} isolated a strain from a case of multiple periarticular abscess; Daddi and di Natale,³⁰ 4 from the sputum, which were suggested as possible "intermediate." Cumming, Foster, Girdwood and Griffith²⁸ reported a strain isolated from the sputum; Griffith and Munro,^{51c} 2 from the sputum; Cellina,²¹ 1 from the kidney at operation; Griffith and Menton,⁵⁰ 2 from bone and joint tuberculosis; and Jensen and Frimodt-Møller^{60d} reported 4 strains isolated from a gland, synovial fluid and pus from cold abscesses.

"Intermediate" Strains. As already pointed out, most workers believe that the type is fixed and that the atypical forms encountered, whether of human or bovine type, are temporary or quasi permanent variants of one or the other fixed types. The so-called "intermediate" strains reported are usually regarded as mixed strains, or as having been derived from spontaneous infection in the experimental animal (Griffith⁴⁹ⁿ).

On the other hand, another group of workers, notable among whom are Calmette, Much, Rabinowitsch-Kempner, Jensen and Frimodt-Møller, believed that there exist transition or intermediate forms between the human and bovine types. The outstanding characteristic of these intermediate types, as pointed out by Jensen and Frimodt-Møller,^{60f} is their lack of stability, both culturally and in the inoculated animal. The early conceptions of Calmette and Much have become obsolete since they were purely theoretical and no experimental work sustained them. There are reported in the literature 48 "intermediate" strains as follows: Rabinowitsch^{104a} reported 6 strains recovered at autopsy (2 in primary intestinal tuberculosis, 1 in generalized tuberculosis of alimentary origin and 3 in miliary tuberculosis). Mohler and Washburn⁸¹ had 1 strain from sputum. Dammann and Rabinowitsch³² reported 1 strain isolated from the skin which culturally was of human type but which possessed an attenuated bovine type of pathogenicity for the rabbit. Duval³⁵ reported 1 strain from the cervical glands; Lindemann,⁷⁴ 1 from the sputum; Rabinowitsch-Kempner,^{105a} 3 from lupus lesions; Aronson and Whitney,⁶ 2 from the lung at autopsy; and Mozer and Mozer,⁸² 3 from bone and joint tuberculosis. These latter writers did not indicate the cultural characters of these strains, but stated that biologically they were of "intermediate" virulence for rabbits, suggesting to the Reviewer that they were probably attenuated bovine strains.

d'Asaro⁷ reported an intermediate strain recovered from a case of multiple bone and joint tuberculosis and suggested a mutation of type, but to the Reviewer his results are most simply explained as due to technical error. Valtis and van Deinse,¹³¹ and Bablet, Valtis and van Deinse⁸ reported 21 strains which they identified as "intermediate" and which they had recovered through guinea pig inoculation, some of the animals subsequent to inoculation having been treated with an acetone extract of the Koch bacillus. (See Negre technique above.) Culturally, these strains suggested an atypical bovine type of the tubercle bacillus, but rabbits inoculated with 1 mg. and 0.1 mg. failed to develop the lesions which would have facilitated the identification of type. They classed these strains tentatively as "intermediate." Bablet and

Bloch⁹ had a strain from the skin. Jensen and Frimodt-Møller⁶⁰ reported 7 strains of tubercle bacilli isolated from the urine, sputum, pleural fluid, gastric washings, sputum and 2 from lupus. In a comprehensive study the authors pointed out the following characteristics of these 7 strains: (a) Four grew less eugonic, but distinctly differed from the bovine type; (b) all 7 strains were of low virulence for the rabbit, like the human type, but in all 7 the authors were able in at least 1 rabbit, and in one instance in 3 inoculated rabbits, to demonstrate bovine tubercle bacilli. They used careful controls against spontaneous and mixed infection, and concluded that the appearance of typical bovine tubercle bacilli in the passage animals were due to the transformation of the original strains.

The term "intermediate" involves the conception of mutation of type. This may appear an attractive theory on purely theoretical grounds, but there has not been enough satisfying evidence to support such a conception. Were it not for Rabinowitsch-Kempner and Jensen and Frimodt-Møller, who are among the most authoritative workers in the field of tuberculosis, one could dismiss these views as being fallacious on various technical grounds. Griffith,⁴⁹ on the basis of vast experience, has failed to bring about transmutation of type under any experimental conditions nor could he obtain any convincing evidence for its occurrence in the natural infection in man. Animal passage using various types of animals and over different periods of time up to 3 years did not bring about any change suggesting transmutation. He took particular care in these experiments against spontaneous infection in his animals which if it had occurred would naturally have confused the issue. There was no certain evidence that the bovine tubercle bacilli change into human bacilli during residence in the human body, but there is ample evidence that they may retain their cultural and biologic qualities after prolonged sojourn in man. Notable in this regard are the typical bovine tubercle bacilli isolated by Griffith⁴⁹ from tuberculosis of the skin, 13 to 52 years after infection (average 22 years) and from many cases of bovine phthisis in the adult dating back to early childhood.

Tuberculosis of the Skin. A striking feature regarding the tubercle bacilli isolated from the skin is that about one-half of the strains of human type and about two-thirds of the bovine strains show a marked degree of attenuation of pathogenicity for both the guinea pig and the rabbit. Calmette²⁰ gave the feature of attenuation of the tubercle bacillus from skin lesions as the reason "why no one has ever been successful in inoculating lupus from one human being to another," although no mention is made of any experiments for this purpose.

There are reported 718 strains of tubercle bacilli isolated from various forms of tuberculosis of the skin. Of this number 503 were of human and 215 (29.9%) of bovine type. A detailed analysis of 375 strains showed that 229 were of human, 134 of bovine type and 12 were listed as "intermediate." Of the 229 human strains, 117 (51%) were typical culturally and biologically, and 112 (49%) were definitely attenuated. Of the 134 bovine strains isolated, 49 (36.6%) were typical culturally and of standard virulence for experimental animals, and 85 (63.4%) were attenuated.

The following are the published reports: Burnet¹⁹ isolated 10 strains of the human type from lupus—of these 9 were of standard virulence and 1 was attenuated; Gossio,⁴⁷ 15 human type strains, all of attenuated virulence; Andersen,⁴ 28 strains, 18 were human tubercle bacilli of which 9 were of standard and 9 of attenuated virulence, and 7 bovine strains of which 4 were of standard and 3 of attenuated virulence. In addition, he had 3 "intermediate" strains. Kirchner⁶¹ reported 23 strains, 11 of human type and 12 of bovine. Of the human strains, 9 were of standard and 2 of attenuated virulence. Of the 12 bovine strains, 5 were of standard and 7 were attenuated in virulence. Rabino-witsch-Kempner^{105a} had 18 strains; of these, 12 were of standard human type, 3 of standard bovine type and 3 strains she classified as "intermediate." Holland⁵⁷ isolated 32 strains of tubercle bacilli, 30 of human and 2 of bovine type. In the 30 human strains 22 were of standard virulence and 8 were attenuated. Of the 2 bovine strains, 1 was of standard and the other of attenuated virulence. Bronstein and Liud-vinovski¹⁸ isolated 17 strains, and of these 13 were of standard human virulence, 2 were of standard bovine type and 2 they classified as "intermediate."

Griffith,^{49p} in a comprehensive study of 188 cases of tuberculosis of the skin investigated by him during the years 1907–1932, found that 95 of the cases were due to the human type of the tubercle bacillus, and 93 to the bovine type. Of the 95 human strains, 34 (35.7%) were culturally and biologically typical, and 61 (64.2%) were attenuated. Of the 93 bovine strains, 31 (33.3%) were culturally and biologically of standard bovine type and 62 (66.6%) were attenuated. Sato¹¹⁵ reported 9 isolations from tuberculosis of the skin, 6 were of human type and 3 of bovine. All the human strains were typical. Of the 3 bovine strains, 1 was of standard bovine virulence and 2 were attenuated. Jensen and Frimodt-Møller,^{60d} in 35 cases of skin tuberculosis, found in 19 the human type of bacillus, in 12 the bovine and in 4 an "intermediate" type. Of the 19 human strains, 3 were of standard virulence and 16 attenuated; of the 12 bovine strains, 2 were of standard virulence and 10 attenuated. Fourteen cases of lupus reported from America gave the following results: Ravenel¹⁰⁷ (who was probably the first to isolate a bovine bacillus from man) obtained a bovine strain; Hess⁵⁶ reported 2 bovine strains; Park and Krumwiede, in 1911,^{94b} 1 human strain; and Lewis,⁷³ 1 bovine strain. Price^{103c} isolated 9 strains, 8 human and 1 bovine. There is no indication that any of these American strains were of other than standard type.

Bovine Phthisis. This term designates pulmonary tuberculosis in man caused by the bovine type of the tubercle bacillus. The most important information recently brought to light is the fact that the bovine type of the tubercle bacillus can and does produce tuberculosis in the human lung. The investigation of this question followed the dogmatic statement of Robert Koch, in 1908, that pulmonary tuberculosis in man was not caused by the bovine bacillus. Up to 1914, outside of the British Isles, there were reported 926 strains of tubercle bacilli isolated from the sputum. All of these were of the human type and in only 3 instances bovine strains were also present.

In the British Isles, Griffith reported, in 1909, 2 cases of bovine tuberculosis of the lung from England^{49a} and, in 1913, 1 case from

Edinburgh,^{49b} and in 1916 Wang¹³⁵ reported another case from Edinburgh in a man of 41. No new cases were reported from Britain until 1922, when Munro discovered 2 cases of bovine phthisis near Edinburgh (Munro and Griffith⁸⁶). An intensive investigation followed Munro's finding. In Scotland, and later in the north of England, cases came to light relatively quickly and it became evident that bovine phthisis in man occurred much more frequently than had been previously thought possible.

Up to September, 1937, there were reported a total of 320 cases of bovine phthisis. Of this number, 163 have been reported from Great Britain (Table 1).

TABLE 1.—INCIDENCE OF BOVINE TUBERCULOSIS IN MAN IN GREAT BRITAIN. (GRIFFITH.^{49r})

Variety of tuberculosis.	No. of cases.	English statistics.			No. of cases.	Scottish statistics.		
		Percentage of cases infected with bovine type of bacillus.				Percentage of cases infected with bovine type of bacillus.		
		Under 5 yrs.	5 to 15 yrs.	All ages.		Under 5 yrs.	5 to 15 yrs.	All ages.
Cervical gland .	126	90.9	53.4	50.0	93	65.0	62.3	51.6
Lupus (skin) .	191	58.4	44.4	48.7	13	100.0	71.4	69.2
Scrofulodermia .	60	53.3	43.3	36.6				
Bone and joint .	553	29.5	19.1	19.5	218	46.2	28.9	29.8
Genito-urinary .	23	17.4	42	31.0
Meningeal .	265	28.1	24.5	24.6	203	34.4	14.0	29.6
Autopsies. .	187	28.6	15.5	22.5	290	33.6	38.5	32.4
Miscellaneous .	23	33.3	9.1	8.7	14	71.4
Total.		Human.	Bovine.	Bovine.	Total.	Human.	Bovine.	Bovine.
Pulmonary . .	3254	3198	56	1.7%	2051	1944	107	5.2%

TABLE 2.—INCIDENCE OF BOVINE TUBERCULOSIS IN MAN IN DENMARK. (JENSEN AND FRIMODT-MOLLER.^{60b,c})

AND PARASITIC DISEASES.												
			Up to 15 yrs.			15 to 30 yrs.			30 yrs. and over.			
	Total.	Bovine.	%.	Total.	Bovine.	%.	Total.	Bovine.	%.	Total.	Bovine.	%.
Respiratory . . .	1824	88	4.8	432	29	6.7	1007	50	5.0	385	9	2.3
Bones and joints .	567	105	18.5	98	24	24.5	255	57	22.4	214	24	11.2
Glands	251	123	49.0	80	66	82.5	97	47	48.5	74	10	13.5
Meninges . . .	304	75	24.7	176	58	33.0	92	13	14.1	36	4	11.1
	2946	391	13.3	786	177	22.5	1451	167	11.5	709	47	6.6

In Scotland, Griffith and Smith,⁵² Griffith and Munro,⁵¹ Griffith,^{49b} and Wang¹³⁵ reported in all 2051 cases of pulmonary tuberculosis of which bovine tubercle bacilli were found in 107 instances (5.2%). In England, Cumming,²⁷ Edwards, Lynn and Cutbill,³⁸ Griffith and Menton,⁵⁰ Griffith,^{49r} and Cumming^{27c} reported bovine tubercle bacilli in 56 (1.7%) of 3254 cases of pulmonary tuberculosis. In Wales, Cumming found 2 cases (1%) of bovine phthisis in an analysis of 203 cases (included in the English figures) of pulmonary tuberculosis (Griffith^{49r}). The geographic distribution of bovine phthisis in Britain is very interesting. It increases in frequency from the south to the north of England. The highest incidence occurred in northeast Scotland, and has a direct relationship with the incidence of tuberculous infection in cattle as indicated by Griffith.^{49r} In striking contrast with the English,

Welsh and Scottish findings are the findings of Cumming^{27c} for the Irish Free State. In an examination of 320 cases of pulmonary tuberculosis, not a single bovine strain of the tubercle bacillus was recovered. It is perhaps significant in this regard that Coffey²³ considered that bovine tuberculosis in the Irish Free State was definitely under control.

In Denmark, Jensen and Frimodt-Møller^{60b} recovered 88 strains of bovine tubercle bacilli from among 1824 cases of pulmonary tuberculosis (4.8%). The distribution of bovine phthisis in Denmark is very instructive: only 1.6% occurred in Copenhagen and the islands; 5.4% in north and east Jutland, and 13% in west and south Jutland, the distribution corresponding directly with the prevalence of tuberculosis in cattle. In Holland, in 468 cases of pulmonary tuberculosis studied, 29 (6.2%) proved of bovine origin. Ruys^{111a} found bovine tubercle bacilli in 3 out of 115 cases in Amsterdam, and in 10 out of 89 adults in north Holland, giving a percentage of 6.4 for her 204 cases.

TABLE 3.—THE INCIDENCE OF BOVINE TUBERCULOSIS IN MAN.

Country.	Total number.	Human.	Bovine.	Bovine, %.
France ^{5, 9, 26, 33, 68, 108, 109, 112b, 132}	1083	1055	28	2.6
Germany ⁶⁷	1165	1007	158	13.5
Netherlands ^{14, 72, 111, 133}	767	701	66	8.6
Switzerland ^{106, 117, 124}	218	201	17	7.8
Sweden ⁶⁴	14	14	0	0
Norway ^{3, 11, 67, 126}	107	101	6	5.6
Poland ¹⁰¹	160	149	11	6.9
Italy* 7, 21, 29, 30, 47, 98, 116	871	846	25	2.9
Spain ²⁵	95	90	5	5.3
Hungary ^{58, 128}	334	328	6	1.8
Greece ²	327	327	0	0
Australia ^{97, 139}	280	246	34	12.1
Japan ^{1, 62, 63, 78, 115, 141}	272	264	8	2.9
United States ^{5, 22, 39, 40, 45, 46, 56, 73, 76, 79, 92, 93, 94, 107, 120, 121}	1362	1202	160	11.7
Canada ¹⁰³	901	847	54	6.0

* In Italy there were 64 atypical strains.

In Germany, in an analysis of 495 cases of pulmonary tuberculosis, 16 (3.2%) proved of bovine type. Most noteworthy is the work of Lange^{66c} who reported 12 cases in this series. He particularly emphasized the fact that 8 of the 12 cases of bovine tuberculosis of the lung occurred in individuals whose occupation brought them in close contact with cattle, such as milkers, stablemen and so on. In Italy, Daddi,²⁹ Daddi and di Natale,³⁰ and Savagnone,¹¹⁶ and Pergola⁹⁸ reported that in 639 cases studied they found 16 (2.4%) of bovine type. In Hungary, Szüle (1936)¹²⁸ reported 2 cases of bovine phthisis in 206 cases studied (0.9%). In Switzerland, Strempel and Mündel¹²⁴ reported 1 case in 60 studied. In France, from a total of 561 cases, Saenz^{112a} and d'Arcier and Mme. d'Arcier-Borrel⁶ reported 2 of bovine type (0.4%). In Poland, Piasecka-Zeyland,¹⁰¹ of 112 cases studied, reported 3 (2.7%) of bovine type.

Of great importance is the work done by Griffith^{49r} and his collaborators in the survey of bovine phthisis in Great Britain. In 67 of the cases reported he isolated the organism himself and 95 strains were submitted to him for further study by Munro, Cumming and Lynn.

In 13 cases the results of the sputum examination were also confirmed by isolating in each case identical strains at autopsy. Two cases yielded mixed human and bovine bacilli; 5 strains isolated in this series showed attenuation in virulence—the remaining 8 strains were culturally and biologically typical bovine. The extent of tuberculous involvement in these cases of bovine phthisis varied from a limited lesion in one lobe to widespread bilateral disease; and in character from acute exudative tuberculosis to chronic fibrosing disease, lasting many years and in some instances becoming quiescent and sputum negative. Bovine phthisis is clinically and radiographically indistinguishable from infection due to the human bacillus. Of the 13 cases that came to autopsy, 8 showed evidence of disease in the mesenteric glands—obviously older than the lesion in the lung. The anatomic evidence strongly favored the alimentary tract as the portal of entry in these cases. In 5 of the remaining 13 the portal of entry was not conclusive. Griffith reported 4 further cases of alimentary tuberculosis with pulmonary cavitation in the lung due to bovine bacilli. The bacilli were recovered from the organs after death but had not been obtained from the sputum during life. Three occurred in children under 5 years, and 1 in an adult of 21, with bilateral cavitation in the apex of each upper lobe. Thus, in the opinion of Griffith⁴⁹ and his collaborators, the portal of entry of the tubercle bacillus in bovine phthisis is by the alimentary tract—usually as a childhood infection and the dissemination occurs by the blood stream, in contrast to human phthisis where the portal of entry is by the respiratory tract.

Lange,⁶⁶ on the other hand, believed that the infection of the lung with the bovine tubercle bacillus is often an inhalation infection through contact with tuberculous cattle, and occurs in adult life. Tobiesen, Jensen and Lassen¹²⁹ agree with the British workers regarding the portal of entry by the alimentary tract, but they cannot overlook contact infection as a possibility. In this regard they pointed out that Blegvad and Jensen (1935) isolated bovine tubercle bacilli from 6 cases of primary tuberculous conjunctivitis in milkers.

There is *no* convincing evidence of human-to-human transmission of bovine tubercle bacilli (Walker),¹³⁴ but there is clinical and anatomic evidence of alimentary infection. In fact, Griffith^{49r} stated that in Britain, at least, bovine phthisis is caused by infection acquired in childhood, adolescence or even adult life, through the consumption of infected cow's milk.

Milk in Its Relation to Tuberculosis in Man. The incidence of bovine tuberculosis in man depends upon the amount of tuberculous infection in cattle with its subsequent milk infection, and is directly influenced by the custom prevailing in the community of feeding infants and children raw milk. Milk can be contaminated from the cow in a number of ways: 1, Indirectly by contamination of the milk, while milking, with droplets or dust from the sputum, or from the dust of dried feces of the infected cow; 2, directly by the bacilli from lesions in the cow's udder. This is the less common but much more dangerous form of contamination. Table 4 is merely a collection of condensed statistics on the findings of tubercle bacilli in raw milk. Most of these results no longer represent the present-day condition, many are too few to be of any statistical value, but in a broad way the table suggests

the extent of the danger of infected milk. The circumstantial evidence is so strong that few question that milk is the source of the infections in human cases; direct proof in specific cases is rare, but has been accomplished by Park and Krumwiede,⁹⁴ and Price.^{103d} There have been at least 2 human experiments using bovine tubercle bacilli. Weber,¹³⁶ in an experiment to confirm Koch's contention that the bovine tubercle bacillus was of low pathogenicity for man, fed 360 individuals, of whom 151 were children, with raw milk from tuberculous cows. Only 2 cases of cervical adenitis developed in this group. Szampan,¹²⁷ in Zürich, reported the development of a cold abscess at the site of an intramuscular inoculation of milk in 2 infants.

TABLE 4.—BOVINE TUBERCLE BACILLI IN RAW MILK. (GERVOIS.⁴³)

	Number.	Bovine.	%.
South of England	12,324	917	7.4
North of England	39,620	3228	8.1
Scotland	21,461	979	4.5
United States	1,476	126	8.5
Canada	200	8	4.0
Argentine Republic	17	3	17.6
India (Bombay)	600	0	0.0
Australia	1,016	1	0.09
Germany	3,395	289	8.5
Denmark	28	4	14.2
Spain (1936)	200	16	8.0
France	58	6	10.3
Greece	35	0	0.0
Italy	544	37	6.8
Netherlands	200	4	2.0
Poland	297	67	22.5
Russia	73	3	4.1
Switzerland	245	20	8.1
	<hr/> 51,789	<hr/> 5708	<hr/> 6.97

The evidence for milk as a source of the bovine infection in man has been accumulated by workers all over the world. Fraser⁴² pointed out that among the children with bovine infection a large number had been fed raw milk. Mitchell⁸⁰ found in a group of 19 patients fed raw milk, bovine tubercle bacilli from the cervical glands in 17. Griffith, in England,^{49r} Griffith and Summers,⁵³ and Munro and Walker,⁸⁸ in Scotland, Park and Krumwiede⁹⁴ and Chang,²² in the United States, Price,^{103c} in Canada, and Boer,¹⁴ in the Netherlands, have drawn attention to contaminated milk as the source of tuberculous infection in children. In Poland, Piasecka-Zeyland and Sznajder¹⁰² mentioned a case of bovine tuberculosis in a patient of 24 years who until the age of 15 years had had raw milk. Tobiesen, Jensen and Lassen,¹²⁹ in Denmark, emphasized that 13 of the 26 cases of bovine phthisis they investigated gave a similar history. Strempel and Mündel,¹²⁴ in Switzerland, pointed out their cases of bovine infection had been fed raw milk. In Aberdeen, Griffith and Smith⁵² found that 12 out of the 13 patients with bovine phthisis were in the habit of drinking raw milk. Ruys^{111a} noted the same conditions in 23 of 33 cases of bovine tuberculosis in Amsterdam. In France, Lesné, Saenz, Salembiez and Costil⁷⁰ found that 8 of the 9 cases of tuberculous meningitis in children caused by the bovine tubercle bacillus had been fed raw milk, and they all

lived in rural districts. Munro and Scott⁸⁷ found that the children under 2 years who died of tuberculous meningitis had been fed raw milk. They stressed in their cases the lack of contact with known human tuberculosis and concluded that milk was the source of the infection.

Griffith^{49r} stated for England that "5 to 12 per cent, and more, of samples of ordinary milk contain tubercle bacilli, and more than one third of the milking cows in this country are tuberculous," while in northeast Scotland he reported, in 1936, that 40 to 90% of the cows in 6 milking herds reacted to tuberculin and in one small district no less and 15 of 53 cows in one herd showed udder tuberculosis. Dalrymple-Champneys³¹ stated that no less than 80% of the samples of milk brought to London in tanks for pasteurization were infected with tubercle bacilli. In Denmark, as already mentioned, this same relationship has been shown to exist between bovine infection in man and the disease in cattle.

Control of Bovine Tuberculosis in Man. The part taken by bovine strains of tubercle bacilli in the problem of human tuberculosis is no longer questioned. Bovine tuberculosis in man can be completely eliminated in one of two ways: 1, the eradication of the disease in its natural host by tuberculin testing and the slaughter of reactors; 2, by the universal pasteurization of all milk used for human consumption.

The application of the first of these methods in the United States had resulted (Wight)¹⁴⁰ in the very striking reduction from an incidence of 10% infection in cattle in 1908 to 0.7% in 1936. In 1918, there were 4.9% reactors; in 1924, 3.2; in 1928, 2.3; in 1929, 1.8; in 1930, 1.7; in 1934, 1.6; in 1935, 1.5; and in 1936, only 0.7%. The result in 1936 involved the testing of 23 million cattle. In this same year among 10 million cattle (not including reactors) slaughtered for food evidence of tuberculosis was found in only 0.19%. It would seem that this marked reduction in bovine tuberculosis has been reflected in the striking drop in the death rate from extrapulmonary forms of tuberculosis in man from 22 per 100,000 in 1916 to 5 per 100,000 in 1937 (Smith).¹¹⁹ The figure shown in Table 3 indicating an incidence of 11.7% for bovine tuberculosis in man in the United States has been influenced by the recent results reported by Chang²² from Lakeville State Sanatorium (Massachusetts). The Reviewer cannot believe that his figure represents the situation in the United States today in that of his 200 cases, 55 (27.5%) were of bovine type. The results of Park and Krumwiede⁹⁴ and Park⁹³ show from 564 cases an incidence of 7.6% bovine infection, while the results of Aronson and Whitney⁶ and van Es³⁹ give 3.8 and 3.9%. It is highly desirable in view of the splendid results obtained in the eradication of tuberculosis in cattle that a great many more statistics should be obtained for the United States showing the incidence of bovine infection in man both in pulmonary and extrapulmonary infections.

As an example of the efficacy of supervised pasteurization of milk the city of Toronto offers the best example available in the literature. Since 1916, when pasteurization was made compulsory, there has not been a single proven case of bovine infection in the generation of children using the city milk. Price^{103d} bases this contention on a bacteriologic study of nearly 500 tuberculous children.

In reviewing the incidence of bovine infection in man in the various countries it is to be noted that the correlation is often very poor between bovine infection in cattle and the incidence of the bovine type of infection in man. France, Greece and Poland are striking examples showing this lack of correlation. The explanation for this we believe is to be found in the household custom of boiling milk, as an economic procedure to prevent it from going sour. Thus unconsciously the children of these countries have escaped bovine tuberculosis which is so common in other European countries.

Summary. The bovine tubercle bacillus has been shown to be a factor of considerable importance in human tuberculosis, particularly in children, accounting for approximately 10% of such cases. The distribution, character of the lesions and the outcome of the infection are the same in both types of infection. The most important difference, however, is that the bovine infection can be eliminated by practical methods which have been shown to be highly efficient.

The most important recent advances in our knowledge have been in the studies of bovine phthisis and it has been shown that the relationship between it and the tuberculous infection in cattle in this form of bovine infection in man is essentially the same as in the extrapulmonary forms of the disease.

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HYGIENE AND PUBLIC HEALTH.

UNDER THE CHARGE OF

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THE STATUS OF PERTUSSIS VACCINE IN THE PREVENTION OF WHOOPING COUGH.

IN 1931, the Council on Pharmacy and Chemistry of the American Medical Association voted to omit pertussis bacillus vaccines from the list of new and non-official remedies in view of the fact that in 15 years

of extensive use no acceptable confirmatory evidence for their value had become available. In the past 8 years the whole subject of the use of pertussis vaccines in the prevention of whooping cough has been reviewed. Some of the reasons for previous failures have become apparent. Definite progress has been made and recent studies indicate that it is possible by artificial immunization to increase definitely the resistance against infection and to prevent, or to reduce the severity of, clinical attack.

Etiologic Relationship of *H. pertussis*. The rationale of the preventive use of pertussis vaccine depends fundamentally upon the primary etiologic relationship of this organism to the disease whooping cough. In 1932, Rich reviewed the evidence and found it unconvincing. He called attention to a number of considerations which were consistent with the hypothesis that the disease was primarily due to a virus which paved the way for secondary invasion by *H. pertussis*, *H. influenza*, and possibly other organisms. Without reviewing these considerations in detail, it suffices to state that subsequent work has failed to establish the existence of the hypothetical virus, and, on the other hand, observations on experimental animals and human beings have confirmed the case for *H. pertussis* as the primary incitant (Farber and Wolbach,⁸ 1932; Sprunt, Martin and Williams,²⁷ 1935; Rich *et al.*,²¹ 1932; MacDonald and MacDonald,¹⁷ 1933; Miller,¹⁸ 1933; and Gallavan and Goodpasture,⁹ 1937). While it is undoubtedly true that pertussis-like coughs may occasionally be caused by atypical organisms such as *B. parapertussis* (Eldering and Kendrick,⁷ 1938; and Bradford and Slavin,² 1937), *A. bronchisepticus* (Brown,³ 1926), and possibly also *H. influenza* (Rich,²⁰ 1932), such studies as those of Gardner and Leslie¹⁰ (1932), Kristensen¹³ (1933), Sauer²² (1933), and Kendrick and Eldering^{12a} (1935) have shown beyond all question that *H. pertussis* is the organism commonly associated with this condition.

Methods of Producing Pertussis Vaccine. The primary etiologic relationship of *H. pertussis* having been established, successful immunization waits upon the development of an effective antigen. Although Sauer and others had empirically used freshly isolated strains, the fundamental necessity of this requirement was emphasized by the work of Leslie and Gardner¹⁶ (1931). They pointed out that although *H. pertussis* is a uniform species without fixed varieties or types, when it is subcultured on artificial media it tends to go through a series of regressive changes corresponding to the smooth→rough variation which has been found to occur with many other species of bacteria. They described 4 phases in this change, Phases 1 and 2 being identified with the smooth, and 3 and 4 with the rough colony variation. Their observations have been confirmed in all important essentials by Shibley and Hoelscher²⁴ (1934), Toomey, Ranta and Takacs²⁸ (1935), Lawson¹⁵ (1939) and others. It has been established that with the variation toward the rough colony type the organism tends to lose its capsule, is altered antigenically, becomes less toxic for guinea pigs, rabbits and mice, and is no longer infective for the chimpanzee (Shibley.²³ 1934).

This variation afforded an explanation for the failure of the vaccines formerly produced. It became clear that the primary requisite for an effective pertussis vaccine was the use of freshly isolated and Phase 1 strains.

Because of previous failures, Sauer also advanced the idea that it was necessary to increase the dosage from 3 injections, with a total of 22,000,000 bacteria or less, to a dosage of 70,000,000 to 80,000,000 bacilli or more, given in 3 or 4 bilateral injections at intervals of 1 week. It was pointed out that full protection could not be expected until 2 to 3 months after the vaccine was injected. The discussion in this paper is confined to vaccines made and administered according to these general principles to prevent or modify clinical attack.

Laboratory Appraisal of Immunizing Value of Vaccines. No laboratory method has yet been devised which is satisfactory for assay of the immunizing value of a pertussis vaccine. The production of agglutinins, opsonins, precipitins, and complement fixing antibodies in animals is obviously inadequate. Burnet and Timmins,⁴ Bradford,¹ Powell and Jamieson,¹⁹ Silverthorne,²⁵ Lawson¹⁵ and others have explored the possible use of white mice. It has been shown that they can be actively immunized by injection of a suitable antigen. The test for the presence of immunity carried out later—production of pneumonia after intratracheal injection or production of death after intraperitoneal injection—is so crude and variable that it is as yet far from satisfactory.

It has long been known (Gundel, Keller and Schlüter,¹¹ 1935; and Kristensen and Larsen,¹⁴ 1926) that complement fixing antibodies and/or agglutinins can be demonstrated in a very large proportion of patients with whooping cough 3 or 4 weeks after onset. Daugherty-Denmark⁵ (1936) has found these antibodies present in the serum of patients a month or more after the third injection of Phase 1 pertussis vaccine. It has not yet been proved, however, that their appearance is a necessary accompaniment of active resistance to the disease, nor that their absence is an indication of susceptibility.

Clinical Appraisal of the Immunizing Value of Vaccines. Lacking satisfactory laboratory test, the immunizing value of a pertussis vaccine *can only be determined by human trial*. The conditions of this trial must be such as to permit unbiased judgment. This implies that along with a large group of injected children an equivalent group of non-injected controls must be kept under observation, that the opportunity to detect and definitely diagnose clinical attacks of whooping cough must be equal in the two groups; that the period at risk must be the same; and that the length of time must be sufficient to afford opportunity for a significant and equally distributed number of natural exposures to occur. As all who have had experience know, this is an ideal which can be approached but never completely realized in dealing with human beings under natural conditions. Nevertheless, there have become available during the past 7 years a number of reports of studies of the immunizing value of Phase 1 pertussis vaccine which present evidence worthy of note.

Sauer began his observations in 1928 and has published a series of reports, modifying his procedure from time to time. In 1937 he gave a summary of the experience of Evanston's municipal whooping cough clinic. During a 3-year period, 1122 children with an average age of 10 months had completed pertussis vaccinations. The nurses of various agencies in close daily contact with contagious disease situations reported to the Department of Health (*i. e.*, discovered) that 128 of these children had subsequently been exposed—94 within the house-

hold and 34 outside the family—to other children who had whooping cough. Six injected children (4.7% of those so exposed) developed the disease. The clinical course in 5 was mild, in 1 it was quite severe. Sauer did not present for comparison an equivalent group of non-injected children in this publication. Recourse must be taken to general experience. It is conceded that ordinarily 70% or more of young children who have not been immunized may be expected to contract whooping cough when exposed to another case within the household. Sauer's most recent experience (1939) is summarized in the following tabulation:

CONTROLLED VACCINATIONS WITH AUTHORIZED *HEMOPHILUS PERTUSSIS* VACCINE*
(JANUARY 1, 1933, TO OCTOBER 1, 1938), AGE RANGE 6 MONTHS TO 4 YEARS.

			Contracted whooping cough.		
Groups.			No.	No.	%.
Private, from 1933		Unvaccinated (controls)	560	105	18.8
		Vaccinated	1001	16	1.6
Evanston Dept. of Health from 1934		Unvaccinated (controls)	1100	129	10.8
		Vaccinated	1377	10	0.7
St. Vincent's (1935 epi- demic)		Unvaccinated (controls)	70	52	74.2
		Vaccinated	75	6	0.8
Totals		Unvaccinated (controls)	1730	286	16.5
		Vaccinated	2453	32	1.3

* Since March 1, 1938, only "double strength" vaccine (1 cc. = 20,000 organisms) has been used; total dosage from 80,000 to 100,000 million.

The article does not contain a definite statement as to the comparability of test and control groups. It is not clear just how long these children have been kept under observation, to what extent they have suffered exposure, and how effective the machinery was for detecting the clinical attacks which occurred in both groups. If comparability be conceded then the frequency of attack among the unvaccinated was about 12 to 13 times that of the vaccinated group. The net observation of 2453 vaccinated children over periods varying from a few months to 5 years, with only 32 clinical attacks of whooping cough having been reported among them in a city the size of Evanston, would seem in itself to imply that a considerable degree of resistance must have been conferred.

Since 1932 a comprehensive program of study of the immunizing value of pertussis vaccine has been under way in Grand Rapids, Mich. A progress report was made by Kendrick and Eldering,^{12b} in 1936, and the final analysis^{12c} was presented at the 1938 meeting of the American Public Health Association. The total time period covered by the observation is 44 months. There was gradually accumulated an inoculated and a control group of children of the age range 8 months to 6 years. They were admitted and discharged from the study after varying periods of time, and while in the study kept under observation and checked by repeated nursing visits. Final analysis was based upon 1815 children, representing 2268 person-years of experience, in the injected group, and 2397 children, representing 2307 person-years of experience, in the control group. While the average period of observa-

tion for the whole group was 13 months, 25 % of the children were under observation less than 6.5 months and 75 % less than 17.7 months. Detailed statistical comparisons indicated that the test and control groups were similar in respect to conditions affecting susceptibility and exposure to pertussis infection. The attack rate (expressed upon the basis of 100 persons at risk for 12 months) was 2.3 in the injected and 15.1, or more than 6 times as great, in the control group. The difference is about 15 times the standard error. By various other methods of comparison, the advantage was found to be consistently in favor of the injected group. For example, among 83 of the injected group who were exposed to infection within the household, 29 (34.9 %) developed clinical attacks, while among 160 of the control group similarly exposed, there were 143 (89 %) attacked. The data are convincing that vaccine as made and administered in this study afforded a considerable degree of immunity against clinical attack for a period of approximately 1 year.

In 1934, Doull, Shibley and McClelland⁶ set up a study of active immunization against whooping cough in Cleveland. An interim report was made in 1936; final report is in press. Between June, 1934, and July, 1935, 483 Cleveland children between 6 and 15 months of age were given whooping cough vaccine. All save 61 received full dosage. A total of 496 children of comparable ages and living in the same neighborhoods were selected as controls. Children of both groups were kept under careful observation from June 24, 1934, to September 12, 1936. There had occurred 61 attacks among inoculated and 71 among control children. Thus the attack rate during this period was not significantly lower among the inoculated, although there was some evidence that their attacks were milder than in the non-inoculated.

The evidence was collected so carefully in this study that one cannot escape the conclusion that the injection of pertussis vaccine—as prepared by these authors—had very little, if any, effect in preventing clinical attack, although it may have reduced severity.

At Stanford University School of Medicine Children's Clinic, a study in pertussis immunization has been going on since 1935. A preliminary report was given by Miller in 1938. Up to the time of the report 206 children had been enrolled in the injected group and 181 in the control group. The great majority in both were babies between 6 and 10 months of age at the time of entrance into the study. They were apparently followed through clinic visits. In the test group there have been 26 known exposures and 8 cases; in the control group, 19 known exposures and 29 cases. The crude attack rate % in the former is 3.9 % as compared with 16 % for the latter. Presumably the information is equally complete (or deficient) with regard to both groups.

Since 1935 a similar study has been in progress in the out-patient department of the University of California, upon which Singer-Brooks²⁶ has made a preliminary report. Immunizing injections were given to children more than 5 months of age. Sibling controls were used rather than alternate patients. Definite appointments for follow-up visits were given at regular intervals of 3 or 4 months. Histories of exposures were requested and investigated. During a period of 5 years there have accumulated 272 children who received the total dosage of pertussis vaccine and 256 non-injected have been followed as controls. Among the injected children, there have been reported 42 definite

exposures and 7 clinical attacks. Among the control group, there have been reported 71 definite exposures and 62 cases. By chance, the control group have been exposed to a somewhat greater degree than the injected group, but the difference in attack rates (2.5% for the injected as compared with 24.2% for the control group) is such as to suggest strongly that the procedure had conferred a considerable resistance against infection.

Silverthorne and Fraser²⁵ reported, in 1938, upon a study which has been in progress at the Hospital for Sick Children in Toronto. Children have been inoculated at the hospital's county branch over a period of 5 years; other children at the county branch, who for some reason were not suitable for vaccination, have been selected and followed as controls. They have been under observation over variable periods of time by public health nurses, or reported upon by a group of physicians in private practice. Among 161 control children there have been 27 "direct" contacts and 23 of these developed whooping cough. In the vaccinated group of 747 children there have been 41 instances of "direct" contact and 2 cases of whooping cough have developed.

Admitting the variable definition of the word "control" in these several studies, the uncertainty surrounding the distribution of exposures and detection of clinical attacks, and the rôle which chance or selection may play in the comparisons, the evidence from the repeated trials points very strongly in one direction, with the exception of the Cleveland experience. The question naturally arises whether in this study the vaccine used differed in some important detail from those used in the others.

Differences in the Vaccines. All used the same method of injection and approximately the same dosage. The vaccines were made from several freshly isolated Phase 1 strains grown for 72 hours on Bordet-Gengou medium, with some differences as to blood content. The bacteria were chemically killed with merthiolate or phenol. The single detail in which there was apparently a significant difference was in regard to the method of suspending the organisms. Sauer, Miller, Singer-Brooks, and Silverthorne scraped the growth off with physiologic salt solution and standardized without washing. Kendrick and Eldering washed off the growth in normal saline, filtered through a thin layer of cotton, centrifuged, discarded the supernatant fluid and resuspended the organisms in saline. Doull, Shibley and McClelland incubated for 48 hours, scraped off the colonies, washed once in sterile distilled water, and resuspended in 0.85% sodium chloride. It is possible, though not proved, that this procedure resulted in a vaccine suspension which was poor in the effective antigenic substance which is peculiar to Phase 1 pertussis bacilli. This substance has not yet been clearly identified, nor are the conditions of its production understood. Further studies of the biology of the organism in this regard are needed.

The method of production of pertussis vaccine is largely empiric and accordingly subject to variation. Until there is a satisfactory laboratory method for assay of immunizing value, there probably will be a considerable difference in the vaccines commercially produced.

Since variation in the amount of effective antigen in a vaccine cannot yet be controlled, attempts to fix the dosage by human trial are subject to imponderable error. The same consideration interferes in attempts

to determine the earliest age at which vaccines can be given, the duration of the resistance conferred, and the necessity for repeating the antigenic stimulus at intervals. Conclusions on these points are premature in the light of evidence at present available.

Summary. Since 1931 additional observations have been accumulated which establish the rôle of *H. pertussis* as a primary incitant of whooping cough. After recovery from human sources the organism tends to undergo regressive changes from a smooth to a rough phase when subcultured on artificial media. Concomitant with this is a gradual loss in immunizing properties. It has been learned empirically by trial on children that an effective vaccine can be made from freshly isolated strains possessing the characteristics of the smooth (Phase 1) variant. The degree of resistance conferred is variable. The studies available do not permit an exact quantitative statement, but range in estimate from very little (Cleveland experience) to almost complete (Evanston) protection. Since the method of injection and the total dosage employed was approximately the same in all the studies, it is inferred that the variability may in part be due to difference in the detail of preparing the antigenic suspension. The effective antigenic substance peculiar to Phase 1 has not yet been definitely identified. The conditions under which maximum yield may be obtained are unknown. Until these have been clarified, only vaccines made and used with strict adherence to the principles set forth above can be expected to confer a considerable degree of resistance. The procedure seems to be relatively free from objectionable reaction. Although severe reactions are occasionally observed, especially in young infants, these are no more so than would be expected with equivalent amounts of any bacterial suspension.

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PHYSIOLOGY

PROCEEDINGS OF
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SESSION OF JANUARY 16, 1939

The Effect of the Insulin Shock Treatment for Schizophrenia on Glucose Tolerance. JOHN W. APPEL and JOSEPH HUGHES (Laboratory of the Pennsylvania Hospital, Department for Mental and Nervous Diseases). Sixty-two glucose tolerance tests were performed on 30 patients receiving insulin treatment for dementia præcox. In this treatment, daily injections were given over a period of 2 months, the daily dose ranging from 50 to 200 units of insulin; the average total insulin dosage was 4000 units. All glucose tolerance curves obtained were within normal limits. High curves developed during the treatment. Maximum rises as high as 230 mg. per 100 cc. venous blood were obtained. This maximum rise usually occurred $\frac{1}{2}$ to 1 hour after the ingestion of glucose. All curves, however, had returned to below 115 mg. per 100 cc. by 3 hours. There were 2 exceptions to this. In 7 cases a curve was obtained before and after insulin treatment, and in each of these cases the curve after treatment showed a greater maximum rise than the curve before treatment. No curve failed to show this rise during the course of treatment. In 11 cases a high curve was observed following treatment which thereafter fell to lower levels. In but a single case the curve was found to be not elevated shortly after treatment and showed no significant change at subsequent observations. Most curves had fallen to the pre-insulin level by 3 months. No low curves characteristic of increased tolerance were obtained. A possible basis of these findings could be a temporary inhibition of the secretion of insulin by the pancreas as a result of insulin treatment.

The Fundamental Effects of the Camphor Group. WERNER L. LIPSCHITZ (Laboratory of Pharmacology, University of Istanbul). The mechanism of the action of camphor (borneol, menthon, hexton) was investigated using other tissues than the heart: uterus, intestine, arteries, bronchial muscle. The excised rabbit intestine, when exhausted by 4 hours' work, can be stimulated by camphor. When effective or subthreshold concentrations of camphor were combined with other stimulant or depressant drugs, merely additive effects were observed. On respiring erythrocytes it was found that the curve which plots the degree of effect against the camphor concentration is a biphasic one: by low concentrations the rate of respiration is increased, by higher concentrations it is depressed. If the camphor is removed by repeated washings with saline, the depressant effect not only disappears but the respiration of the stimulated, and even of the previously narcotized, cells is increased above the normal rate (carbohydrate oxidation). The camphor stimulation outlasts the presence of the drug. It pro-

duces a new state of the cell, altering the hydrophil catalytic cell structure. This selective camphor stimulation was found on erythrocytes of the normal, or repeatedly bled, goose and of the rabbit, and on surviving liver slices. It was not found on the non-living (hydrophobe) Warburg model of the respiration (charcoal + oxalic acid). On respiring erythrocytes the same three phenomena of camphor action appear as on the surviving heart: the depression useful in the case of supernormal function, the stimulation useful in cases of deteriorated function, and the persistence of the augmentory action—"Nachbesserung."

Further Studies on the Ballistocardiograph (An Apparatus for the Recording of the Heart's Recoil and the Blood's Impacts in Man). ISAAC STARR (Hartzell Department of Therapeutic Research, University of Pennsylvania). Further studies have been made on the ballistocardiograph as a mechanical instrument. Due to vibration periods existing in the human body the descending part of the ballistic curve is an unreliable index of the forces applied. The ascending part is reasonably reliable but it should be corrected for overshooting if the waves are in phase with the body's period.

Abnormal types of ballistocardiogram encountered in patients with heart disease may be derived theoretically from abnormal curves of blood velocity in the aorta. Curves of similar abnormal types have been produced in acute animal experiments by asphyxia, by chloroform and by injuring the right ventricular wall.

When the ballistocardiogram has an abnormal form the formula which permits calculation of cardiac output from the normal record may not be employed. However, new constants for the old formula may be derived theoretically.

The old equation may be written in the following form:

$$(\text{Cardiac output})^2 = K (\text{altitude of most conspicuous up wave} + \text{altitude of most conspicuous down wave in mm.}) (\text{aortic cross-section area in cm.}^2) (\text{duration of cardiac cycle in sec.}) (\text{duration of ejection in sec.}).$$

When the form is normal $K = 370$. For various extremely abnormal forms K has been calculated to range from 690 to 800. For intermediate forms, intermediate values should be taken.

As abnormal forms of ballistocardiogram occur infrequently, except in very sick persons, the opportunity of comparing the cardiac output calculated from the abnormal ballistocardiogram with that obtained by other methods has come infrequently. In 3 cases there was reasonable agreement with results obtained by ethyl iodide.

The Effect of Variations in the Electrolytic and Water Composition of the Body on Anaphylaxis in Guinea Pigs. MITCHELL I. RUBIN and MILTON RAPAPORT (Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania). Male guinea pigs weighing about 250 gm. were passively sensitized to horse serum. The first part of the experiment was concerned with attempts to reduce the severity of the anaphylactic shock. In this group of animals a

dose of serum was used which resulted in death from anaphylaxis in 22 of 25 control animals.

I. In a group of 20 animals depleted of sodium chloride (with no dehydration) by the technique of Darrow and Yannet, the mortality from anaphylactic shock was significantly reduced; only 4 of the 20 animals died. This reduction in mortality is comparable to that obtained in a previous study, where animals were dehydrated by water restriction prior to the administration of the shocking dose of horse serum.

II. In a group of 24 animals given 0.8 to 1 cc. of isotonic potassium chloride intravenously prior to the shocking dose, 13 of the animals survived (a significant figure).

III. A group of 20 animals given magnesium chloride intravenously or magnesium sulphate subcutaneously was protected to a significant degree; 13 of the animals survived. In the survivors, complete muscular relaxation was obtained; in the other animals, no relaxation was apparent prior to the injection of the shocking dose of antigen.

The second part of the experiment involved the exaggeration of the anaphylactic response. In this experiment, a dose of serum was used which killed but 1 of 20 control guinea pigs. In a group of 20 animals rendered edematous by subcutaneous and intraperitoneal injection of normal saline, there was a significant increase in mortality from anaphylactic shock, 7 of the animals dying.

Correction: In the article by Levy, Bruenn and Russell (February issue, p. 244), Dr. Levy requests us to note that under the caption "Normal" (third paragraph) the first sentence should read: "Partial or complete reversal of the direction of T in Lead I, in the absence of any $RS-T$ displacement in this lead, is of uncertain significance. It was observed in 2 of 66 supposedly normal persons." It should also be noted that in Figure 5, the December, 1937, record should precede instead of follow that of February, 1938.

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THE
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APRIL, 1939

ORIGINAL ARTICLES.

THE INFLUENCE OF ACID AND ALKALINE SALTS UPON THE
BLOOD IN HYPOCHROMIC ANEMIA TREATED BY
IRON PARENTERALLY.

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MANY investigators agree that achlorhydria interferes with the absorption of iron in certain cases of iron-deficiency anemia. Mettler and Minot³ demonstrated that in cases of chronic hypochromic anemia iron administered orally produced more rapid hemoglobin regeneration when the gastroduodenal contents had a low rather than a relative high pH. Recent studies by Kellogg and Mettler² indicate that in some anemias due to chronic blood loss from peptic ulcer the alkalization process associated with a Sippy regimen inhibits the absorption of iron contained in food. The following observations were made in order to determine if the oral administration of acid or alkaline salts in sufficient quantity to alter significantly the pH of the urine, affected the *utilization* of parenterally administered iron. Under the conditions of the experiments the influence of the acidity of the gastro-intestinal tract upon the absorption of iron was eliminated.

Method. Eleven cases of hypochromic anemia, or iron deficiency, were studied. Table 1 gives a brief clinical résumé of these cases.

The patients received a basal diet low in iron. The reticulocytes were counted daily. Venous blood was obtained every other day and prevented from clotting with oxalate. The number of red blood cells, hemoglobin percentage and, according to the method of Wintrobe, the hematocrit, mean corpuscular volume and mean corpuscular hemoglobin concentration were determined on this blood. The hemoglobin was determined with the Sahli apparatus calibrated so that 100% hemoglobin was equivalent to 15.6 gm. per 100 cc. of blood, or 20.9 vol. % oxygen capacity (Van Slyke).

The observations on each of the cases followed a preliminary control period of about 1 week, during which time it was observed that the hemoglobin and hematocrit values remained stationary and that the percentage of reticulocytes was not significantly elevated. In all cases obvious blood loss had ceased for at least one

TABLE 1.—SUMMARY OF 11 CASES OF HYPOCHROMIC (IRON DEFICIENCY) ANEMIA.

Case No.	Age.	Sex.	Initial R.B.C. (in mil.).	Initial hemo-globin, %.	Etiologic factors and remarks.
1	76	F	3.06	32.5	Uterine bleeding; poor diet; edentulous; gastric anacidity after injection of histamine.
2	19	M	1.975	33.5	Chronic blood loss from duodenal ulcer; gastric hyperacidity.
3	59	F	3.24	39.0	Chronic blood loss from carcinoma of colon; gastric anacidity after injection of histamine.
4	47	F	2.92	24.0	"Idiopathic" hypochromic anemia; menorrhagia; dysphagia; poor diet; gastric anacidity after injection of histamine.
5	58	M	3.06	48.0	Chronic blood loss from duodenal ulcer; chronic alcoholism; asymptomatic tertiary syphilis; normal gastric acidity.
6	31	M	2.06	33.0	Chronic blood loss from duodenal ulcer; normal gastric acidity.
7	63	M	3.34	31.0	Chronic blood loss from carcinoma of stomach; gastric anacidity after injection of histamine.
8	36	M	3.13	58.0	Chronic blood loss from duodenal ulcer; normal gastric acidity.
9	45	F	2.79	26.0	"Idiopathic" hypochromic anemia; menorrhagia; hemorrhoids; gastric anacidity after injection of histamine.
10	79	F	4.045	44.5	Malnutrition; low gastric acidity after injection of histamine.
11	48	M	4.05	29.5	Chronic blood loss from duodenal ulcer; gastric hyperacidity.

week before control observations were begun and there was no evidence of blood loss during the periods of observation. Guaiac tests were performed on the stools daily. After the control period iron was administered intramuscularly in the form of green iron and ammonium citrates (U. S. P.), 0.1 gm. daily or twice daily for a 20- to 32-day period. Some patients occasionally experienced toxic reactions with the larger dose. During the first half of this period the patient was given 24 gm. of sodium bicarbonate by mouth daily. This was given in 6 equal doses at 3-hour intervals during the day. During the second half of the period of iron therapy the patient was given 4 gm. of ammonium chloride by mouth daily, divided in 4 equal doses at 4-hour intervals. On 2 occasions this procedure was reversed.

With the basal diet which the patients received, the pH of the urine could be readily changed with acid or alkaline salt in the amounts mentioned above. During the period of alkali therapy the urine pH was maintained at 8 or above and during the period of acid therapy at 6 or below.

Results. Each of the 11 patients showed a gain in weight during the 10- to 16-day period of alkalization and in some instances obvious edema developed. The average weight gained during this period was 7.4 pounds per individual. The greatest weight gain of

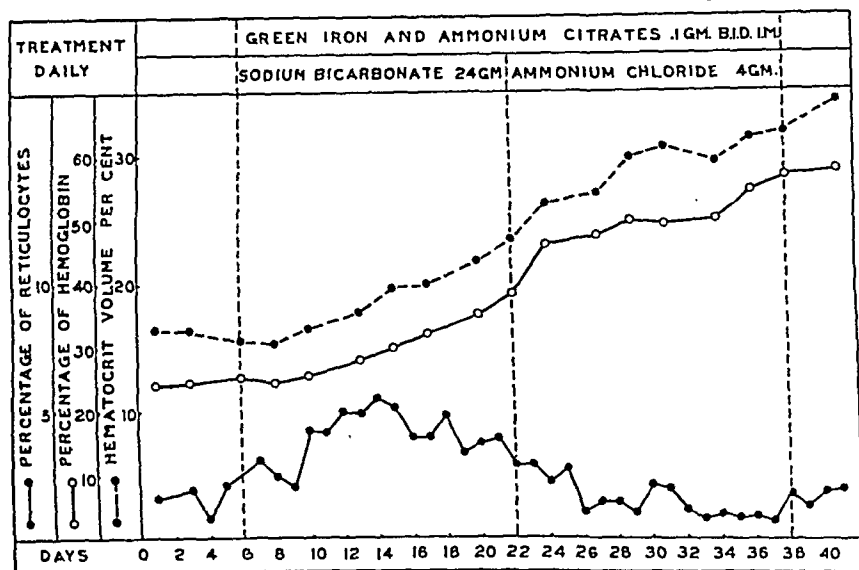


FIG. 1.—Case 4 (Tables 1 and 2). This figure shows the influence of the oral administration of alkaline and acid salts upon blood formation, in a case of hypochromic anemia receiving iron parenterally. There was an initial reticulocyte response to the administration of iron and an increase in the hemoglobin and hematocrit values. Note the "apparent" more rapid hemoglobin formation during the period in which the acid salt was given but the absence of any second reticulocyte response.

any one person was 15 pounds. Conversely, all individuals showed a reduction in weight while receiving the acid salt. This was especially marked when the 10- to 16-day period of acid medication immediately followed the period of alkali therapy. The average weight lost during the acidifying period was 6.1 pounds per individual. These observations are in accordance with the results of other workers on the effects of a high sodium or high ammonium chloride intake, particularly in the presence of protein deficit.

Figure 1 shows the pertinent hematologic data in a typical case. In all instances the rise of hemoglobin was more marked during the time the acid salt was fed. When the data for all the cases were tabulated to represent a single average case the increase in

hemoglobin was 5.3% during the alkalization period and 9.2% during the acidification period of the same duration. For various reasons, however, it cannot be concluded from this that the utilization of injected iron was greater when an acid salt was administered than when an alkaline salt was given.

It was observed in all instances that there was a rapid increase in hemoglobin and hematocrit values upon shifting from alkaline to acid salts. It was also noted that with a shift from neutral to alkaline and from acid to alkaline there was always a small immediate decrease in the hemoglobin and hematocrit values. It, therefore, appears that the regeneration of hemoglobin was *not* more rapid when the acid salt was given but that the greater increase of hemoglobin was due to a shift in plasma volume. A reticulocyte response

TABLE 2.—UTILIZATION OF INTRAMUSCULARLY ADMINISTERED IRON IN 11 CASES OF HYPOCHROMIC ANEMIA.

Case No.	Estimate of total grams circulating iron before treatment.	Estimate of total grams circulating iron after treatment.	Total grams iron administered.	Per cent utilization of iron.*
1	0.890	1.539	0.730	89
2	1.323	1.971	0.730	77
3	0.951	1.278	0.608	54
4	0.537	1.213	0.973	69
5	1.194	1.548	0.426	83
6	1.469	1.766	0.441	67
7	0.683	0.918	0.385	61
8	1.436	1.853	0.502	83
9	0.564	1.070	0.699	81
10	0.827	1.208	0.608	63
11	0.832	1.209	0.730	52
Average	70

was observed in all cases when iron was first administered, but a second reticulocyte response never occurred when the acid salt was substituted for the alkaline one. The abrupt rise in the hemoglobin value observed during the period of acid salt administration is quite different from the usual gradual response of hemoglobin to iron administered by the parenteral route. Evidence from 2 cases not included in this report suggests that this phenomenon occurs regardless of whether iron is given or not.

The percentage utilization of iron given intramuscularly in these cases compares favorably with that shown by Heath, Castle and Strauss,¹ and Whipple and Robscheit-Robbins.⁴ The observations were not carried out quite long enough after the cessation of iron therapy to obtain the complete rise of hemoglobin which the injected iron might have been capable of producing. An approximation of the total grams of circulating iron in the blood before and after treatment was calculated from the hemoglobin values and the blood volume. It was assumed that hemoglobin contains 0.35% iron.

The blood volume was calculated by multiplying the square meters of body surface, obtained from the height and weight, by 2423.¹ In the 11 cases studied, the utilization of the injected iron ranged from 52 to 89%, with an average of 70% (Table 2). Two additional cases of hypochromic anemia which were unsuitable for the acid and alkaline salt studies, because of chronic gastro-intestinal hemorrhage, showed only 29 and 32% "utilization" of injected iron.

Comment. The present observations demonstrate that the administration of either an acid or alkaline salt does not affect the utilization of injected iron in patients with hypochromic anemia. Sudden shifts in the hematocrit values occurred coincident with changes in the pH of the urine and body weight. The evidence at hand suggests that these sudden changes were due to changes in plasma volume and not to improved or impaired utilization of the injected iron. Since the iron was administered intramuscularly, the possibility of the acidity of the gastroduodenal contents affecting the absorption of the iron was eliminated. To avoid errors in drawing conclusions regarding hemoglobin regeneration from iron therapy, in cases with iron deficiency, it must be recognized that the acidity of the diet when affected by the administration of acid or alkaline salts has a significant influence on the plasma volume. This is especially true when the blood formation is being studied over relatively short periods and the importance of small changes is being stressed.

Although it is rarely necessary to give iron parenterally in an iron-deficient individual, the present observations reemphasize the fact that injected iron apparently is used almost quantitatively for hemoglobin regeneration. When the percentage utilization falls below 50% it strongly suggests concomitant blood loss.

Conclusions. 1. The oral administration of acid or alkaline salts in sufficient quantity to cause significant body weight and urinary pH changes does not affect the utilization of iron injected intramuscularly in cases of hypochromic anemia.

2. The changes in plasma volume accompanying a sodium bicarbonate or ammonium chloride regimen must be considered when conclusions are drawn about hemoglobin regeneration in hypochromic anemia.

3. In 11 cases of hypochromic (iron deficiency) anemia an average of 70% of the intramuscularly administered iron was utilized for hemoglobin regeneration.

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PRESERVED CITRATED BLOOD "BANKS" IN RELATION TO TRANSFUSION IN THE TREATMENT OF DISEASE WITH SPECIAL REFERENCE TO THE IMMUNOLOGIC ASPECTS.

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TRANSFUSION of preserved citrated blood from "banks" has become increasingly popular within recent years. The usual method employed in the United States is that of the Cook County Hospital,³ consisting in the addition of 14 cc. of a sterile 2.5% solution of chemically pure sodium citrate in physiologic saline solution to each 100 cc. of blood, and preservation at 4° to 6° C. in a refrigerator. This gives a 0.35% concentration of sodium citrate for the prevention of coagulation and after typing, sterility and Wassermann tests, the blood is ordinarily available for transfusion over a period of 10 days to several weeks.

Physiologically and according to clinical experience, such preserved citrated blood is apparently satisfactory for the restoration of blood volume and superior to saline, glucose and acacia solutions in the treatment of severe traumatic hemorrhage and shock. Whether or not the erythrocytes are sufficiently preserved to carry on internal respiration is debatable; likewise the question as to whether or not the platelets and coagulating principles are sufficiently preserved for the treatment of the thrombocytopenic purpuras and other hemorrhagic dyscrasias.

While these matters will be considered later, my special purpose is to discuss preserved citrated blood in the treatment of acute and chronic infections with special reference to the septicemias, and I may mention at the outset that available data indicate that it should not be used for these purposes when more than 2 to 3 days old.

The Immunologic Aspects of Transfusion. It is sometimes stated that the chief value of blood transfusion in the treatment of septic states with or without associated septicemia is to combat the secondary anemia and that it is not indicated or required until or unless the hemoglobin is reduced to about 40% with a corresponding reduction in erythrocytes.

With this I do not agree. Septicemia at least is apparently the result of a breakdown or exhaustion of the normal clearing mechanism of the blood, not infrequently the result of continuous accession of bacteria and their toxic products from foci of infection of the fixed tissues. I have gradually gained the conviction that one of the most important reasons for frequent transfusions in the treat-

ment of septic states, and especially those with an associated septicemia, is to furnish specific and non-specific immune substances in the blood of the donor, which may have become reduced or exhausted in the hard-pushed patient or recipient. Furthermore, it is not unlikely that the leukocytes of *fresh* blood may serve a useful therapeutic purpose. Therefore, without questioning the value of transfusion in septic states from the standpoint of combating secondary anemia, it seems to me that proper emphasis must be placed upon its possible additional value from the immunologic standpoint and if this is true, the therapeutic status of preserved citrated blood should be examined from both angles.

Briefly and in general terms it may be stated that normal or natural resistance and immunity to infection is due in part to specific antitoxins and such sensitizing antibodies as agglutinins, opsonins and bacteriolysins that may be present in the blood. To these, from the non-specific standpoint, must be added complement, leukins (from leukocytes) and plakins (from platelets). Among these the opsonins are of particular importance because of the rôle they play in phagocytosis, not only by the microphages of the blood and fixed tissues, but by the cells of the reticulo-endothelial system as well. Furthermore, agglutinins likewise facilitate both phagocytosis and bacteriolysis *in vivo* and complement is especially important in both particulars, while the leukins and plakins are apparently largely responsible for the normal non-specific bactericidal activity of the blood. Indeed it would appear that the chief therapeutic value of non-specific immuno-transfusions conducted by the intravenous injection of the donor with 100 million killed typhoid bacilli in vaccine a few hours before transfusion is due in part not only to the transfer of more than normal numbers of leukocytes from donor to patient but likewise to additional amounts of these normal or natural non-specific bactericidal substances.

Certainly we have ample data for indicating that these specific and non-specific mechanisms are responsible for the remarkable capacity of the blood for normally clearing itself of organisms and especially because of phagocytosis by the cells of the reticulo-endothelial system. In septic states, especially septicemia, it is a logical deduction that this clearing mechanism is reduced or exhausted. If this is true, one of the purposes of transfusion in treatment should be to supply the hard pressed patient with as many of these specific and non-specific factors as possible. One cannot now state that natural antitoxins for the several exotoxins of staphylococci and streptococci are reduced or exhausted in acute infections and especially septicemia, but this may be logically inferred. While it is admittedly difficult to measure complement in relation to bacteriolysis, yet this is comparatively easy in relation to hemolysis and I am convinced on this basis that it is frequently reduced below average normal levels in staphylococcus and streptococcus septi-

cemias. Indeed, I believe that one of the purposes of transfusion is to supply the patient with the complement of the donor; and I believe the same applies to opsonins, which likewise have been found to undergo reduction below average normal and especially in acute fulminating infections.

Additional observations on the total bactericidal activity of whole blood for staphylococci, streptococci, pneumococci and *B. typhosus* have indicated that in a large percentage of cases there is a demonstrable reduction. This, however, I have never been able to measure with acceptable accuracy; but it is probably due not only to reduction in complement and opsonins, but probably to bacterioly-sins and the non-specific leukins and plakins as well.

If one of the purposes of transfusion in the treatment of septic states is to supply the patient with these specific and non-specific immunologic principles, in addition to combating secondary anemia, the question at issue is whether or not transfusion supplies them in amounts of therapeutic value, in view of the fact that normal blood admittedly carries but small amounts of these substances. Indeed, the difference of opinion that exists on the clinical value of transfusion in the treatment of acute and chronic infections is largely on this basis. Insofar as specific antibodies are concerned, it would appear that the blood of convalescent or actively immunized donors is to be preferred on the basis of supplying larger amounts, and for this reason specific immuno-transfusions are always to be preferred when possible.

Furthermore and especially in relation to preserved citrated blood in "banks" for the treatment of acute and chronic infections, and especially septicemias, the important question is whether or not immune bodies, as well as functionally active erythrocytes and platelets are sufficiently preserved to be of value. My own studies have been mostly confined to complement, opsonins, total bactericidal activity and the phagocytic activity of neutrophils; insofar as these are concerned the results have indicated that preserved blood is apparently of no value after 2 to 3 days' preservation, as previously stated.

Effects of Sodium Citrate on Complement. As is well known, human complement deteriorates rapidly, even when kept at 4° C. unless special methods for preservation are employed. For example, as shown in Table 1, the complement of the sera of 3 specimens of human blood left on the clots and kept at 4° C. in a refrigerator showed marked deterioration at the end of 5 days.

Deterioration, however, is observed to a much lesser degree in citrated human blood kept at 4° to 6° C. Opponents to the citrated or indirect method of blood transfusion have advanced the objection that sodium citrate in 0.25 to 0.35% concentration is destructive for human complement. This, however, does not appear to be true; indeed, the reverse appears to be the case as sodium citrate

in 0.35% concentration apparently preserves the complement of human blood in a remarkable degree, analogous to the preservation of guinea pig complement for the Wassermann test by sodium

TABLE 1.—THE HEMOLYTIC ACTIVITY OF SERUM LEFT ON CLOTS AND KEPT AT 4° C.

Intervals.	A.	B.	C.
Immediately	0.1*	0.1	0.05
24 hours	0.1	0.1	0.1
48 "	0.1	0.1	0.1
72 "	0.1	0.2	0.1
5 days	0.4	0.5	0.4
7 "	†		

* Approximately smallest amount of serum giving complete hemolysis of 0.5 cc. of 2% suspension of sheep corpuscles sensitized with 2 units of hemolysin.

† No hemolysis with 0.5 cc. of serum (the largest amount employed).

acetate and sodium chloride. For example, as shown in Table 2, the hemolytic activity of the complement for sensitized sheep corpuscles in the citrated (0.35%) bloods (kept at 4° to 6° C.) of 6

TABLE 2.—THE HEMOLYTIC ACTIVITY OF PLASMA OF PRESERVED CITRATED BLOODS FOR SENSITIZED SHEEP CORPUSCLES.

Intervals.	A.	B.	C.	D.	E.	F.
Immediately	0.1*	0.1	0.1	0.05	0.05	0.05
24 hours	0.1	0.2	0.1	0.05	0.05	0.05
48 "	0.1	0.2	0.2	0.05	0.05	0.05
72 "	0.1	0.2	0.2	0.05	0.05	0.05
5 days	0.1	0.2	0.2	0.05	0.05	0.05
7 "	0.2	0.2	0.2	0.05	0.05	0.05
14 "	0.3	0.3	0.3	0.15	0.05	0.05
21 "	0.3	0.3	0.3	0.25	0.1	0.1

* Approximately smallest amount of plasma of citrated bloods preserved at 4 to 6° C. giving complete hemolysis of 0.5 cc. of 1 to 2% suspension of sheep corpuscles sensitized with 2 units of antisheep hemolysin.

donors showed some reduction 24 to 48 hours after collection in 2 of them (B and C), but in general terms the activity of the complement of all 6 was well preserved up to 2 to 3 weeks (longer periods not being employed) when some deterioration was observed.

TABLE 3.—THE PRESERVATION OF GUINEA PIG COMPLEMENT WITH 0.35% SODIUM CITRATE AT 2° TO 4° C.

Intervals.	Citrated complement.	Control complement.
Immediately	0.05*	0.05
24 hours	0.05*	0.05
48 "	0.05*	0.05
72 "	0.05*	0.05
5 days	0.05*	0.1
7 "	0.05*	0.2
14 "	0.1	0.4

* Approximately smallest amount of complement giving complete hemolysis of 1 cc. of 2% suspension of sheep corpuscles sensitized with 2 units of antisheep hemolysin.

The same has been found true of guinea pig complement, as shown in Table 3. In this experiment a portion of the pooled complement sera of 3 guinea pigs was kept at 2° to 4° C. and showed

some deterioration in hemolytic activity for sensitized sheep corpuscles at the end of 5 days, whereas a citrated portion (0.35%) kept under identical conditions and titrated for hemolytic activity at the same intervals and under identical conditions showed no deterioration until about 14 days.

At first, I thought that these results might be due to hemolytic activity on the part of sodium citrate itself; but, as shown in Table 4, even 1 cc. of a 50% solution in normal saline equivalent to 0.5 gm. was without hemolytic effects for 0.5 cc. of a 1% suspension of washed sheep cells in a total volume of 3 cc. at 37° C. in a water bath for 1 hour. Furthermore, when portions of the citrated plasmas of the 6 donors (listed in Table 2) were heated in a water bath at 55° C. for 30 minutes at the end of 14 days' preservation at 4° to 6° C., it was found that hemolytic activity for sensitized sheep corpuscles was completely lost, even in doses as high as 0.5 cc. of undiluted plasma, indicating that heating had inactivated the plasmas presumably because of destruction of complement.

However, 0.2 to 0.3 cc. of a 5% solution of sodium citrate were destructive or anticomplementary for 0.4 cc. of 1 to 30 guinea pig complement (Table 4). It is apparent, therefore, that sodium citrate is destructive for guinea pig complement in high dilutions, but that 0.35% is much less destructive for undiluted guinea pig and human complements.

TABLE 4.—THE HEMOLYTIC AND ANTICOMPLEMENTARY EFFECTS OF SODIUM CITRATE.

Hemolytic activity.		Anticomplementary activity.*	
50% sol., cc.	Hemolysis.	5% sol., cc.	Hemolysis.
0.1	—†	0.05	No effect; C.H.‡
0.2	—	0.1	No effect; C.H.‡
0.3	—	0.2	Slight effect; M.H.
0.4	—	0.3	Marked effect; N.H.
0.5	—	0.4	Marked effect; N.H.
0.6	—	0.5	Marked effect; N.H.
0.7	—	0.6	Marked effect; N.H.
0.8	—	0.7	Marked effect; N.H.
0.9	—	0.8	Marked effect; N.H.
1.0	—	0.9	Marked effect; N.H.

* Effects on the hemolytic activity of 0.4 cc. of 1 to 30 guinea pig complement for 0.5 cc. of a 1% suspension of sensitized sheep corpuscles in a total volume of 3 cc. at 37° C. for 1 hour.

† No hemolytic effects on 0.5 cc. of 1% suspension of washed sheep corpuscles in a total volume of 3 cc. at 37° C. for 1 hour.

‡ C.H. = complete hemolysis; M.H. = marked hemolysis; N.H. = no hemolysis.

Effect of Sodium Citrate on the Bactericidal Activity of Preserved Blood. The normal or natural bactericidal activity of whole blood *in vitro* may be ascribed to: (a) the presence of specific bacterioly-sins requiring the presence of complement for their activity; (b) non-specific bactericidans (probably leukins and plakins) which are effective without the presence of complement; and (c) phagocytosis by the neutrophils aided by opsonins which are quite similar to complement in their physical properties.

Three-cc. amounts of the citrated blood (0.35%) of 3 donors were placed in 3 sterile test tubes immediately after collection and seeded with 1 drop of 18- to 24-hour broth culture of *S. aureus*, a beta hemolytic streptococcus of Group A and *B. coli* respectively. The blood cultures were incubated at 37° C. for 48 hours, after which they were examined by stained smears and the amount of growth estimated by the number of organisms found. The 3 citrated bloods were kept at 4° to 6° C. and the tests repeated at the intervals up to 21 days (Table 5).

TABLE 5.—THE BACTERICIDAL ACTIVITY OF WHOLE PRESERVED CITRATED BLOOD.

Intervals.	Donor A.			Donor B.			Donor C.		
	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.
Immediately	+	*	+	+	+	+	+	+	+
24 hours	+	+	+	+	+	+	+	+	+
48 "	+	+	+	+	+	+	+	+	+
72 "	+	+	+	+	+	+	+	+	+
5 days	+	+	+	+	+	+	+	+	+
7 "	++	+	++	+	+	+	+	+	+
14 "	++	+	+	+	++	+	++	++	+
21 "	++	++	++	++	++	++	++	++	++

* + = scanty growth; ++ = moderately heavy growth.

It will be noted that even the fresh citrated bloods of each donor seeded with the 3 organisms immediately after collection were not completely bactericidal as scanty growths occurred in all. But at the end of 7 to 21 days (longer intervals not being employed) all 3 citrated bloods kept at 4° to 6° C. showed some loss in total bactericidal activity for one or more of the organisms employed. This reduction in bactericidal activity may have been due to gradual inactivation of complement and opsonins, some loss of bacteriolysins and the non-specific leukins or plakins or all of these, as the tests were of such a character as only roughly to measure the total antibacterial activity of the 3 citrated bloods; but at all events the results indicate that citrated blood kept at 4° to 6° C. tends to lose in total antibacterial properties in from 7 to 21 days.

Effect of Sodium Citrate on the Phagocytic Activity of Preserved Blood. Opsono-phagocytic tests were conducted with 3 citrated (0.35%) bloods employing *S. aureus*, a beta hemolytic streptococcus (Group A) and *B. coli* according to the method of Boerner and Mudd¹ immediately after collection and at the intervals up to 21 days (kept at 4° to 6° C.), shown in Table 6.

A slight reduction in phagocytic activity was noted in some instances 24 hours after collection and citration of the 3 bloods, but more marked reduction was noted in some instances as early as 72 hours after collection. This became more marked on or about the fifth day, followed by almost total absence of phagocytosis on and after the seventh day of preservation.

Similar results were observed in the opsonic indices for all 3 organisms with the blood of Donor A (Table 7).

These marked changes in the opsono-phagocytic activities of the 3 citrated bloods preserved at 4° to 6° C. may have been due in part to deterioration of opsonins, but undoubtedly were mainly and most likely entirely due to autolytic changes in the neutrophils. Indeed, these changes were already well pronounced on the fifth day and so marked by the seventh as to make the phagocytic determinations very inaccurate or entirely impossible.

TABLE 6.—THE PHAGOCYTIC INDICES OF PRESERVED CITRATED HUMAN BLOOD.*

Intervals.	Donor A.†			Donor B.			Donor C.		
	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.
Immediately . . .	38	11	16	10	13	20	28	17	22
24 hours . . .	32	10	14	10	19	22	24	14	18
48 " . . .	31	12	15	12	12	21	21	16	20
72 " . . .	32	9	12	10	8	5	15	11	14
5 days . . .	26	4	9	6	2	1	12	5	8
7 " . . .	—‡	—	—	—	—	—	6	—	3
14 " . . .	—	—	—	—	—	—	—	—	—
21 " . . .	—	—	—	—	—	—	—	—	—

* Percentage of phagocytic polymorphonuclear neutrophils (100 cells examined).

† S. aureus; beta hemolytic streptococcus (Group A); B. coli.

‡ Examinations could not be made because of autolytic changes in neutrophils.

TABLE 7.—THE OPSONIC INDICES OF PRESERVED CITRATED BLOOD OF DONOR A.

Intervals.	Staph. aur.	Beta hemolytic strept.	B. coli.
Immediately . . .	1.5*	0.3	1.0
24 hours . . .	1.5	2.0	2.2
48 " . . .	2.5	1.5	2.1
72 " . . .	1.5	1.0	0.5
6 days . . .	0.2	—	0.1
14 " . . .	—	—	—
21 " . . .	—	—	—

* Average number of organisms per phagocyte; — = examination could not be made because of autolytic changes in the neutrophils.

Effects of Sodium Citrate on the Cellular Elements of Preserved Blood. This led to a more detailed study of changes in the cellular elements (erythrocytes, leukocytes and platelets) of preserved citrated (0.35%) bloods of donors kept at 4° to 6° C. with special reference to the leukocytes.

Immediately after collection and citration of the blood of Donors D, E and F, listed in Table 2, smears were made and stained; smears were also prepared at the intervals up to 14 days shown in this table.

These were examined by Dr. Frank W. Konzelmann, who reported as follows: "Forty-eight hours after collection the *erythrocytes* already showed some evidence of disintegration indicated by swelling and the presence of shadowy forms poor in hemoglobin. At later intervals these changes were more pronounced along with the presence of shrunken or pyknotic cells so that by the end of 14 days almost 30% were shadows with loss of some hemoglobin, swollen and apparently very fragile. The *leukocytes* began to show evi-

dences of disintegration with reduction in numbers as early as 24 hours after collection and after 48 hours the chromatin showed less distinct nuclear markings while the cytoplasm became basophilic. Finally at the end of 14 days the cytoplasm had become completely destroyed with only swollen masses of chromatin remaining. The *platelets* showed distinct clumping immediately and 24 hours after collection with evidence of deterioration in the latter. At the end of 48 hours they became scarce and after 5 days only blue chromatin masses remained."*

A macroscopic examination of the plasma of Donors C, D, E and F secured by centrifuging 3 cc. amounts of blood immediately after collection and at the intervals up to 21 days (Table 8) showed no

TABLE 8.—SPONTANEOUS HEMOLYSIS OF CITRATED BLOOD KEPT AT 4° TO 6° C.

Intervals.	Hemolysis.			
	Donor C.	Donor D.	Donor E.	Donor F.
Immediately . . .	None	None	None	None
24 hours	None	None	None	None
48 "	None	None	None	None
72 "	None	None	None	None
5 days	Very slight	None	Very slight	None
7 "	Slight	Slight	Slight	Slight
14 "	Marked	Marked	Marked	Marked
21 "	Marked	Marked	Marked	Marked

demonstrable amounts of free hemoglobin until about the fifth day of preservation which became more definite by the seventh day and quite marked by the end of 2 and 3 weeks. None was frozen so that hemolysis could not be ascribed to alternate freezing and thawing. It is highly probable that hemolysis began at earlier intervals than those recorded, because the readings were based entirely on naked eye appearance of the plasma and ordinarily is not detectable until the blood is centrifuged.

Differential leukocyte counts were made of the citrated bloods of Donors D, E and F immediately after collection and at the intervals up to 14 days shown in Table 9. On account of the disintegrative morphologic changes, beginning as early as 24 to 48 hours after collection and citration, no attempt was made to differentiate lymphocytes from monocytes but these are listed in the table under the designation of "mononuclear cells." It will be noted that in all 3 of the specimens the neutrophils showed reduction in numbers as early as 24 hours after collection and citration. The percentages of

* While this paper was in course of publication, J. E. Rhoads and L. M. Panzer (The Prothrombin Time of "Bank Blood," J. Am. Med. Assn., 112, 309, 1939) found on the basis of the Quick method, that blood that has been in a bank a week or more would be practically useless in the treatment of the acute prothrombin deficiency encountered in jaundiced patients not adequately treated with vitamin K and bile salts. In their opinion, blood in a bank for 3 days would probably be of some slight value but would be so inferior to freshly drawn blood that they recommend that only the latter be used when transfusion is intended to combat the hemorrhagic tendency in jaundice.

"mononuclear cells" are only approximate; fluctuations and apparent increase in numbers has been probably due to the fact that nuclei of neutrophils with degenerated and lost cytoplasm have been included under this designation.

TABLE 9.—DIFFERENTIAL LEUKOCYTE COUNTS OF PRESERVED CITRATED BLOOD.

Intervals.	Neutrophils.			Mononuclear cells.			Eosinophils.			Basophils.		
	D.	E.	F.	D.	E.	F.	D.	E.	F.	D.	E.	F.
Immediately	29*	56	59	70	43	41	0	1	0	1	0	0
24 hours . . .	9	42	43	91	55	55	0	1	1	0	2	1
48 " . . .	9	24	28	91	76	72	0	0	0	0	0	0
72 " . . .	12	36	—	88	64	—	0	0	—	0	0	—
7 days . . .	7	40	—	93	60	—	0	0	—	0	0	—
14 " . . .	5	44	34	93	56	66	1	0	0	1	0	0

* Percentages: 50 to 100 cells counted.

Discussion. Without attempting any review of the literature on the properties of whole blood by direct transfusion *versus* citrated blood in the treatment of hemorrhage, the hemorrhagic diseases, acute and chronic infections and so on, it may be stated that the results of this study have not revealed any important changes in the cellular or immunologic contents of citrated blood used immediately or within a few hours of collection for transfusion purposes. To the best of my knowledge and experience *fresh* citrated human blood is just as applicable as whole blood by direct transfusion, although I believe the former yields a somewhat higher incidence of febrile and minor reactions.

But the results of the study seriously question the advisability of using citrated blood preserved for 2 to 3 days or longer. Unger⁶ has stated that sodium citrate inactivates complement, renders erythrocytes more fragile, reduces opsonin and destroys the phagocytic activity of the neutrophils. Drinker and Brittingham² state that it renders erythrocytes more fragile and produces suggestive changes in the platelets. Mellon, Hastings and Casey,⁵ and Lewisohn,⁴ however, found that sodium citrate did not increase the fragility of erythrocytes or reduce the phagocytic activity of the leukocytes.

As previously stated, I do not believe that sodium citrate in concentration of 0.35% produces deleterious changes quickly enough to question the value of citrated blood given immediately or within a few hours of collection. But the changes apparent in erythrocytes in 48 hours and certainly after longer periods of preservation, should question the value of preserved citrated blood in the treatment of the anemias. Furthermore, since changes were apparent in the platelets both immediately and 24 hours after collection and citration, it is open to question whether preserved citrated blood should be used in the treatment of the thrombocytopenic and other purpuras where one purpose of transfusion is to supply the patient with coagulating principles.

Certainly preserved citrated blood shows sufficient disintegrative

and autolytic changes in the neutrophils to reduce sharply their phagocytic activities after 2 to 3 days' preservation at 4° to 6° C. and to question its value in the treatment of acute infections and especially septicemia, if it is believed, as I do, that the transfusion of healthy active leukocytes contributes an important factor to resistance.

As previously stated the complement of citrated human blood kept at 4° to 6° C. does not undergo any marked inactivation during the first 14 days of preservation but after this time it and the total bactericidal activity of the preserved blood for such organisms as *S. aureus*, beta hemolytic streptococcus and *B. coli* are reduced sufficiently to question the value of preserved blood in the treatment of the acute and chronic infections. Of course this is in regard to whatever value complement, specific (antibodies) and non-specific bactericidal substances (leukins and plakins) have in the treatment of infections with special reference to the septicemias. It is admitted that the amounts transfused in 200 to 500 cc. of blood are sufficiently small to question their value in treatment, but I personally believe that they are helpful and that blood transfusion in the treatment of infection is just as important from this immunologic aspect as it is in combating secondary anemia. At all events it would appear advisable always to select a convalescent or immunized donor whenever feasible, in order to transfuse as much specific antibodies as possible. It is not yet clear whether or not non-specific immunotransfusions are superior in curative activity to plain transfusions, but theoretically at least they should be, if it is granted that the patient derives additional benefit from the infusion of increased numbers of leukocytes as well as increased amounts of leukins, plakins and specific natural antibodies.

At all events, the results of the investigation have left me with the conviction that, while citrated human blood preserved up to 10 to 21 days at 4° to 6° C. may be useful in the treatment of acute hemorrhage and shock for the restoration of volume, it should not be used at all in the treatment of the anemias, hemorrhagic dyscrasias or infections, and certainly not after 2 to 3 days' preservation.

Summary. 1. While sodium citrate is slightly anticomplementary, the complement of citrated (0.35%) human blood, kept at 4° to 6° C., was well preserved for periods up to 14 to 21 days. The same has been found true of undiluted citrated guinea pig complement kept at 2° to 4° C.

2. The bactericidal activity of normal citrated human blood kept at 4° to 6° C. for *S. aureus*, beta hemolytic streptococcus and *B. coli* decreased after 7 to 21 days' preservation.

3. The phagocytic activity of the neutrophils of preserved citrated human blood kept at 4° to 6° C. for *S. aureus*, beta hemolytic streptococcus and *B. coli* was definitely reduced within 72 hours after collection of blood, becoming markedly so on or about the fifth day,

followed by almost total absence of phagocytic activity on and after the seventh day of preservation. This may have been due to deterioration of normal opsonins but was mostly due to autolytic and degenerative changes in the leukocytes.

4. The erythrocytes of preserved citrated human blood kept at 4° to 6° C. showed evidences of swelling and dehemoglobinization as early as 48 hours after collection with progressive degenerative changes up to 14 days when at least 30% were shadows, swollen and fragile.

5. The neutrophils of preserved citrated human blood kept at 4° to 6° C. showed evidences of disintegration with reduction in numbers as early as 24 hours after collection, with progressive disintegrative and autolytic changes up to 14 days (longer intervals of preservation not being employed).

6. The platelets of preserved citrated human blood kept at 4° to 6° C. showed distinct clumping immediately and 24 hours after collection with evidences of deterioration in the latter. At the end of 48 hours they became scarce and after 5 days only blue chromatin masses remained.

7. For reasons discussed it is believed that citrated human blood preserved at 4° to 6° C. may be useful in the treatment of acute hemorrhage and shock for the purpose of restoration of volume, but is inadvisable for the treatment of the anemias, the blood dyscrasias or infections, and certainly should not be employed for these purposes after 2 to 3 days' preservation.

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SULPHANILAMIDE THERAPY IN GONORRHEA.

REVIEW OF LITERATURE AND REPORT OF 298 CASES.

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NUMEROUS reports have shown that sulphanilamide in large doses often effects a clinical cure of acute and chronic gonorrheal urethritis in the male. Various severe blood dyscrasias, cutaneous

and other reactions have occurred, and have served to warn that this drug is not to be used without careful supervision. Some authors have had results that were entirely unsatisfactory (Anwyl-Davies¹); or have had no conspicuous success (Lees¹⁵), and others have had 60% of failures (Johnson and Pepper¹³); and others have claimed that sulphanilamide has revolutionized the treatment of gonorrhea. It is the purpose of the authors to present their results in a comparatively large series of cases (298), and to compare and correlate them with the other large series of cases that have been reported to date.

Dees and Colston,⁷ the first to use sulphanilamide in gonorrhea, reported 47 cases, with 75% of cures. Reuter²³ reported clinical cure in 90% of 100 cases. Erskine, Johnson and Lloyd⁸ reported early and marked improvement, with particularly excellent results when local treatment is used at the same time, in 100 cases. Crean,⁶ using prontosil soluble and sulphanilamide, effected cures in 90 of 100 cases. Johnson and Pepper¹³ had 60% of failures in 64 cases.

Table 1 shows the largest groups of cases as yet reported. In the series of 100 cases or more, of which there are 4, the proportion of cures has been high enough (76 to 90%) to be very impressive, even if one argues that these cases are only temporarily or symptomatically cured. The authors have found substantial confirmation of the

TABLE 1.—RESULTS OF SULPHANILAMIDE TREATMENTS OF GONORRHEA IN PUBLISHED CASE SERIES.

Author.	Number of cases.	Per cent of cures.
Dees and Colston ⁷	47	75
Reuter ²³	100	90
Herrold ¹¹	30	50
Gruetz ¹⁰	36	66
Anwyl-Davies ¹	19	Entirely unsatisfactory
Erskine, Johnson and Lloyd ⁸	100	Early and marked improvement.
Crean ⁶	100	90
Lees ¹⁵	No conspicuous success, too toxic.
Johnson and Pepper ¹³	64	40
Knight ¹⁴	63	63
Orr ²¹	134	87
Graham ⁹	23 males	65
Graham ⁹	13 females	18
Bush ⁴	20	40
Ferguson, <i>et al.</i>	298	76

action of sulphanilamide in effecting a clinical, and probably a permanent bacteriologic cure, in 76% of 298 patients, and agree, with certain qualifications, that sulphanilamide has "revolutionized" the treatment of gonorrhea, at least in the male. The qualifications alluded to have their origin in our ignorance of the proportion of cases which will relapse or become carriers, and in our imperfect understanding of the mechanism of the drug's action and the reason for its failure in 30% or so of cases. Also, there is the possible additional drawback that a failure with sulphanilamide affects

adversely the ability of the patient to react favorably to other means of treatment. This is the belief of Crean.⁶

We have treated 298 sea-faring men, generally between the ages of 20 and 40, and in good physical condition, in the venereal disease wards of the U. S. Marine Hospital at Stapleton, Staten Island, New York. The first 100 patients were studied by the staff of the Venereal Disease Research Laboratory at the U.S.P.H.S. in Stapleton, and made the subject of a report by Van Slyke, Thayer and Mahoney.²⁴ In a group of 17 of these patients, Van Slyke *et al.* carried out special blood and urine studies in an effect to detect the approach of severe toxic manifestations attributable to the drug. These included red and white blood cell counts, hemoglobin content, red cell fragility determinations, spectroscopic examination for methemoglobin and sulphhemoglobin, CO₂-combining power of the plasma, total non-protein nitrogen and NaCl content of the blood. Further, the studies included determination of the blood concentration of sulphanilamide as determined by the method of Marshall, Emerson and Cutting.¹⁹ "As these procedures failed to presage toxic reactions or to display consistent blood changes (with the exception of the CO₂-combining power of the plasma), they were abandoned as a routine and used only as indicated in the remainder of the study" (Van Slyke *et al.*). The studies on the blood concentration of sulphanilamide, however, were influential in determining the increases in dosage decided upon by the research staff and ourselves.

1. *Relative Success in Acute as Compared With Chronic Cases.* Regarding the relative efficacy of sulphanilamide in chronic cases as compared with acute cases, Crean had excellent results (1 failure, a relapse) in 24 chronic cases, and Herrold cured 10 of 12 chronic cases. Reuter had about equal success with chronic as with acute cases. Knight, on the other hand, states that chronic gonorrhea lends itself less easily to relief by sulphanilamide. The Venereal Disease Research Laboratory at our hospital had only 1 failure among 36 chronic cases (97% successes), and had 77% of cures among the acute cases, but among the subsequent 198 patients studied on our wards, the proportion of failures among the chronic cases was slightly higher, and our combined figures for the 298 cases are 73% of successes in the acute cases (210 cases) and 83% successes in the chronic (88 cases), making the proportion of successes for the entire 298 patients 76%. (We regarded infections of less than 28 days' duration as acute cases, and the others as chronic.) It, therefore, seems fair to say, inasmuch as our experience was the same as that of most other investigators, that chronic cases respond to sulphanilamide somewhat more favorably than do acute cases.

It is important to note that the percentage of cures obtained by our Venereal Disease Research Laboratory in the first 100 cases was much higher than the 198 cases subsequently treated. This

can probably be accounted for by the fact that their dosage was considerably larger and continued for a longer time. Our 198 patients were chiefly treated by a definite routine, as will be explained later under the caption "Dosage."

2. *Time of the Disappearance of Discharge.* There is general unanimity regarding the fact that in successful cases the urethral discharge disappears within 5 days of commencing a course of sulphanilamide. In our successful cases, the average time for the cessation of the discharge in the acute cases was 4.9 days, for the chronic 4.3 days.

3. *Period of Hospital Stay.* There is also unanimity regarding the diminution of the period of symptoms and the consequent necessity for medical care. Crean states, "It has reduced the days of sickness to one-third." The hospital stay for our successful cases averaged 15 days whether acute or chronic, and for our failures, 49 days for the acute and 45 days for the chronic cases. Of course, 15 days was generally longer than was absolutely necessary in the successful cases. Many patients were, or could have been, discharged in 10 or even 7 days.

4. *Criteria of Cure.* Johnson and Pepper: Those patients who 10 or more days after the beginning of the treatment had a positive smear or culture, or showed a hazy or cloudy urine in one or both glasses, are classified as failures.

Reuter: "Disappearance of microscopic pus from the urine, absence of pus from the prostate, loss of all symptoms and failure to produce a recurrence."

Orr: In the male: Absence of gross pus or shreds in 1st or 2d glasses, and by demonstration of less than 8 pus cells per oil immersion field in the prostatic fluid.

Crean: First day: Urethroscopy: Injection of gonococcus vaccine, 1 cc. subcutaneously (1 cc. contains 50 million). Injection of 5 cc. of a 1% solution of silver nitrate into anterior urethra. Microscopic examination and culture of any resultant discharge.

Second day: Examination of urine (2-glass test). Examination of prostate and seminal vesicles and microscopic examination of prostatic fluid. Passage of a Clutton's sound, and further examination and culture of any discharge noticed or obtainable the following day.

Van Slyke *et al.*: A moderately sized sound was passed into the bladder and the pendulous portion of the urethra massaged over the sound. If this procedure did not produce recurrence of the discharge, the maneuver was repeated on the following day. After the 2d sounding, the distal part of the penis was cleansed with soap and water, the prostate thoroughly massaged, and the combined urethral-prostatic secretion examined by smear and culture. If found to be negative, the entire procedure was repeated after a 2-day interval. For purposes of lubrication of the sounds, a sterile tragacanth jelly

free from preservatives was used. (It will be noted that this test of cure consumed 5 to 7 days.)

Our criteria: Disappearance of discharge and burning after one course of sulphanilamide (5 days), both glasses clear, smears negative for Gram-negative diplococci (even if extracellular) after the passage of two sounds, with prostatic massage after each, the second sound being passed 2 days after the first. A persistent morning drop, or a few fine shreds when both glasses were clear, or the presence of occasional pus cell in a scanty morning drop, were not construed as making the case a failure, if the other criteria of success were met with.

It is difficult to evaluate the standards of cure quoted. None of these standards is sufficiently trustworthy to guarantee positively against relapse or transmission of the disease; but, on the other hand, any one of them would probably have been considered adequate tests prior to the use of sulphanilamide. The authors believe that, in the great majority of cases that they have considered cured, relapse or transmission of the disease will not occur, but advise precautions against the possibility of transmission to sexual partners for 1 month, and advise alcoholic indulgence (if so inclined) as a test of relapse.

5. *Frequency of Relapses.* In Pepper and Johnson's series, in 15 of the cases in which the discharge stopped rapidly after the onset of treatment, a positive smear or culture was later obtained. In Crean's series of 68 acute cases, there were 2 relapses; 1 relapse of 24 chronic cases. In Knight's series, 10 of 63 out-patients and 5 of 60 in-patients had relapses. Herrold had 10 cures of 12 chronic patients, and followed the cured patients for 1 to 3 months, without evidence of infection. Van Slyke *et al.* told cured patients to return frequently for observation. Almost half of them (43) returned for observation at periods ranging from 15 to 134 days and now 9 months subsequent to discharge. None of this group has experienced a clinical or bacteriologic relapse. Practically all reported immediate return to hard work and indulgence in alcohol and sexual intercourse. Our total number of relapses is unknown, for the patients on discharge frequently ship to parts unknown.

It will be seen from the foregoing that a satisfactory clinical cure with sulphanilamide seems in the majority of cases to be a real bacteriologic cure, but that relapses sometimes will occur. This, however, does not detract greatly from the value of sulphanilamide therapy.

6. *Dosage.* Table 2 shows the dosage schemes followed by several authors. Crean's doses are not included, as he used both prontosil soluble and sulphanilamide simultaneously. It will be seen from the table that we have used the most intensive type of dosage of any series, and that subsequent to the series we are now reporting, we have started to use a still more intensive dosage. The

experimental work of Marshall *et al.*¹⁹ has led us to the conclusion that it is wisest to give the drug at 4-hour intervals. Long and Bliss' work¹⁷ tends to show that the mechanism of action is that of bacteriostasis (inhibition of bacterial growth). The concentration desired in the blood is given by different writers at different levels, but a fair average, according to Heterick,¹² is a 10 to 15 mg. per 100 cc. of blood, or 1 to 10,000 or 1 to 7500 concentration.

TABLE 2.—DOSAGE.

Author.	Grains for number of days.	Followed by grs. for No. of days.	Followed by grs. for No. of days.	Approx. total. grs.
Johnson and Pepper ¹³	80 for 2-3	60 for 2-4	30-45 daily for maintenance	
Reuter ²³	40 daily (undetermined period)			
Orr ²¹	80 for 4	40 for 4	20 for 7	640
Knight ¹⁴	80 for 3	60 for 3	40 for 4	580
		Repeated if necessary		
Ferguson <i>et al.</i> (in this series)	120 for 2 (except for 1st 100 cases treated by Van Slyke dosage)	60 for 3	... if necessary	420
		Repeated if necessary		
Ferguson <i>et al.</i> (now)	120 for 4	60 for 3	... if necessary	660
		Repeated if necessary		

Marshall *et al.*¹⁹ plotted curves of blood concentration for different individuals after a single oral dose of sulphanilamide. In his Subject "c," whose curve appears to be an approximate mean of the others, the blood concentration of sulphanilamide reached 7.5 mg. % in 2 hours, and declined to 5 mg. % in 9 hours, after a single oral dose of 50 grains (3.6 gm., .05 gm. per kilo, subject's weight about 155 pounds). At the Venereal Disease Research Laboratory at Stapleton it was found that the administration of the drug at continuous 4-hour intervals seemed the correct method for the maintenance of an adequate concentration of sulphanilamide in the blood stream, and also that concentrations of from 8 to 10 mg. % of uncombined sulphanilamide were sufficient to produce apparent cures in some cases, but concentrations of from 10 to 15 mg. % appeared to be more efficacious. (There were failures at both levels, however).

For these reasons, we gave the drug to our 198 patients through the night as well as in the day, at continuous 4-hour intervals (making 6 doses in 24 hours), giving 120 grains a day for 2 days and then 60 grains a day (gr. x q 4 hours) for 3 days. The other 100 cases were given a dosage much higher than our series of 198 cases, but at the same intervals, every 4 hours (day and night), in accordance with Van Slyke outline. At present, however, we are giving 120 grains per day for 4 days, followed by 60 grains a day for 3 days, in an attempt to reach and maintain a concentration approaching 10 to

15 mg. %, mentioned above as seemingly more efficacious. This dosage (120 grains per day for 4 days, and 60 grains per day for 3 days) and even our former dosage (120 grains per day for 2 days, and 60 grains per day for 3 days) is larger and more intensive than those given by most other authors, but we do not feel that the toxic effects we encountered have rendered these amounts inadvisable. Some cases are continued on treatment for a longer period when well tolerated by the patient.

7. *Toxicity.* Severe and even fatal hemolytic anemias, granulocytopenias and other toxic reactions sometimes occur. However, we have had few serious, but rarely dangerous reactions. There were no hemolytic anemias observed. Workers at the Venereal Disease Research Laboratory failed, in their cases, to find evidence of sulphemoglobinemia or methemoglobinemia. Several of our patients had high fever, cutaneous eruptions, intense cyanosis, rapid pulse and general prostration, but all became well in 1 or more days upon discontinuance of the drug and forcing of fluids. Most of our patients showed some cyanosis and one or more toxic effects, like headache, dizziness, anorexia, lassitude, and insomnia, and often they lost about 5 pounds in weight, but these symptoms generally did not warrant cessation of the course of sulphanilamide. We instructed the nursing staff to withhold the drug whenever the temperature was above 38.2° C. We limited water intake to 1500 cc. a day. Inasmuch as a fall in the CO_2 -combining power of the plasma to 38 to 45% was usual, we frequently gave sodium bicarbonate gr. xv t.i.d., to combat toxic symptoms. When laxatives were necessary, we used enemata or cascara sagrada.

Regarding cumulative effects, we have given several patients 2 to 4 courses of sulphanilamide, each course consisting of 420 grains or more in 5 days, over periods of about 6 weeks, with no ill effects. In fact, 1 patient had 1810 grains (122 gm.) in 31 days, without undue toxicity. This patient incidentally developed an acute epididymitis while under treatment.

Regarding precautions, we feel that hospitalization is strongly advisable.

The authors have been informed that other workers have given very large initial doses (120 grains as a first dose, for example), and subsequent relatively large single doses (as, 60 grains in 1 dose). While this type of dosage may, perhaps, prove valuable we feel that if certain of our patients who became toxic had been given these doses, fatalities might have resulted. We, therefore, feel it safer to proceed with 20 grain doses every 4 hours, especially because there is no urgent need to build up a high concentration within a matter of hours, as may indeed, be of vital importance in some virulent streptococcal or other toxin-producing infections.

8. *Value in Complicated Cases.* Herrold¹¹ treated 4 patients with epididymitis. The swelling and pain disappeared rapidly under

treatment. Reuter²³ had 2 cases arriving with epididymitis, and these subsided within 48 hours. Of 16 patients suffering with epididymitis 3 satisfied our criteria of cure as we treated them with sulphanilamide. The results in the complications of arthritis were indifferent.

9. Does Sulphanilamide reduce the *Incidence of Complications*? Johnson and Pepper¹³ found the development of complications "less than in the routine out-patient treatment of this disease." Only 8 of 27 cases of anterior urethritis became posterior. Crean⁶ found in his control series of 30 patients (27 acute, 3 chronic) treated with irrigations, that 10 of the 27 acute cases developed posterior urethritis, and 2 patients developed epididymitis. Reuter²³ had no case of epididymitis develop among his 100 treated cases. He says, "Those cases which did not improve, did not show any tendency to get worse, and remained stationary."

In our series of 298 patients, only a very small proportion of cases of anterior urethritis became posterior, and only 2 cases of epididymitis and 1 of periurethral abscess developed while under treatment.

10. *Should Local Treatment be Given Simultaneously With Sulphanilamide?* Erskine, Johnson and Lloyd reported early and marked improvement, with particularly excellent results when local treatment is used at the same time. In one-half of our patients, local treatment in the form of injections into the anterior urethra of 0.5% Protargol, t.i.d., was given simultaneously with sulphanilamide therapy. Table 3 summarizes our experience with simultaneous local treatment, and without it.

TABLE 3.—CASES WITH SIMULTANEOUS LOCAL TREATMENT AND SULPHANILAMIDE.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
64	35	25	10	89	45
64% success		71% success		66% success	

CASES WITHOUT LOCAL TREATMENT.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
89	22	48	5	137	27
80% success		90% success		83% success	

It will be seen that combined local and chemotherapy gave us 66% of cures, as compared with 83% of cures by chemotherapy alone.

11. *Comparison of Results in Those who Admit One or More Previous Gonorrheal Infections and in Those who Deny any Previous Infection.* Table 4 shows that of 43 patients denying gonorrhea there were 67% successes, while of 49 who admitted one or more previous attacks, there were 84% of cures with sulphanilamide. This seems to substantiate the opinion of Herrold¹¹ (with reference to acute cases), that the best results seem more probable in patients

who have previously had gonorrhea. This tends to imply that an immune mechanism plays some part.

TABLE 4.
PART A—DENYING PREVIOUS INFECTION.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
25	12	4	2	29	14
67% success		67% success		67% success	

PART B—ADMITTING PREVIOUS INFECTION.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
33	6	8	2	41	8
85% success		80% success		84% success	

PART C—EXCLUDING THE 17 CASES WHICH HAD SULPHANILAMIDE PRIOR TO ENTRY.

Denying previous infection.

Acute:

20 of 25 patients, 80% success

Chronic:

4 of 5 patients, 80% success

Admitting previous infection.

Acute:

32 of 36 patients, 89% success

Chronic:

8 of 9 patients, 89% success

(Figures in Part A include 17 patients who were given sulphanilamide before hospitalization, and so were not included in our results).

13. *Influence of Previous Inadequate Dosage of Sulphanilamide, on the Efficacy of Our Course of Sulphanilamide.* We found 14 patients in which sulphanilamide had been taken prior to our treatment. They had been given the drug by a ship's physician, druggist, and others. Arbitrarily considering doses of less than 60 grains for 5 days, or less than 40 grains for 10 days, as inadequate, and higher doses as "sufficient," we find among the inadequate dosages, 10 patients with 4 cures. From the fact that there were only 4 cures among the 10 previously given inadequate courses, whereas we would expect at least 7 cures among 10 cases who had none of the drug previously, one may surmise that previous inadequate dosage might diminish the chance of satisfactory response to a subsequent adequate course of the drug. This opinion has been expressed by other authors, and it is included here because it is, perhaps, plausible according to bacteriologic theory. If (speaking generally) a concentration of a chemical is attained which is not sufficient to check bacterial reproduction, the bacteria present can sometimes develop an adjustment or tolerance to that chemical, and subsequently continue to multiply even though the concentration is later raised to a higher level, at which their growth formerly would have been checked.

Once an adequate course of sulphanilamide has failed, a subsequent adequate course of the same drug is also likely to fail. This tends to be supported by the fact that the authors have had failures after a third or fourth course. When another treatment like typhoid vaccine or local treatment is interspersed between sulphanilamide a cure has been occasionally effected.

The possibility occurs that some closely related compound might

be found which would prove efficacious as an adjuvant to overcome the bacterial tolerance acquired for the sulphanilamide.

13. *Further Comments on the Problem of Failures.* Regarding the problem of failures, we had 55 patients whom we classified as failures after one course of sulphanilamide (consisting, as noted, of 120 grains a day for 2 days, and 60 grains a day for 3 days). Crean⁶ expressed the opinion that a failure with sulphanilamide caused an adverse effect on the ability of the body to react favorably to other forms of treatment.

To continue on somewhat surer ground, in our 55 failures, a variety of other therapeutic measures was tried, including courses of intravenous typhoid vaccine, gonococcus vaccine or antitoxin, courses of anterior irrigations or injections, and hyperpyrexia. Gonococcus antitoxin was soon discontinued because of serum reactions. After a course of typhoid injections, another course of sulphanilamide was successful in some patients, but failed in others. Hyperpyrexia (the fever-box) was generally tried last, and was generally successful after one or more treatments. In connection with this, it is interesting to note that one author² found that a combination of sulphanilamide and hyperpyrexia simultaneously is more successful than either method alone. Hyperpyrexia is not practical for large numbers of patients but it may be that this combined method will prove valuable in rather resistant cases.

14. *Reasons for Failures.* The reason for the failures we do not know. Toxic reactions in some cases cause temporary withdrawal or permanent discontinuance of the drug, with consequent fall in blood concentration. This has apparently caused failure. Reuter²³ observed, however, that those patients who complain early and bitterly of the side-effects, gave the best response to treatment, while the cases which are counted as failures appear to have had a greater tolerance for the drug. This implies that the minor toxic effects are a manifestation of some form of body response to the drug, and that this body response exerts the curative action. The authors could not correlate the degree of minor toxic effects with the degree of success of treatment.

Insufficient amounts of the drug, or too short a time-period of its administration, are likely reasons for many failures. However, even when adequate courses are given, in both the successful and in the unsuccessful cases, the absorption, the maintenance of a satisfactory concentration in the blood stream, and the rapidity of elimination, were entirely comparable.²⁴

A hypothetical bacterial tolerance to the drug, acquired as a result of previous inadequate dosage (and also adequate dosage in individuals who do not respond), may be postulated to account for some failures on subsequent adequate course of therapy.

Crean⁶ observed that robust patients were more likely to be cured than underweight or anemic-looking patients. Our series of cases

do not seem to substantiate this statement, because we have noted cures and failures in both robust and underweight individuals.

Reuter,²³ in a statement already quoted (namely, "It was felt that perhaps these cases—which did not improve with sulphanilamide therapy, but remained stationary—were destined to be of that severe fulminating type,") seems to us to imply that in some cases, the reason for failure may be an exalted virulence of the particular strain of invading gonococci.

Crean⁶ states that the earlier in the infection the patient was started on prontosil-soluble and sulphanilamide, the greater was the chance of success.

15. *Mode of Action.* The question of the mechanism of action is unsettled, and constitutes a very important and interesting problem. Heterick,¹² gives a good résumé of the history of sulphanilamide, showing that Heidelberger and Jacobs* found in 1919 that para-sulphonamide benzene azo-compounds had bactericidal properties, that Domagk* in 1935 demonstrated positive protection for mice against hemolytic streptococci; that Nitti and Bovet performed similar experiments; that Nitti, Bovet and Trefouel produced a white crystalline organic compound which contained the benzene-sulphonamide group, minus the azo-linkage (sulphanilamide or "prontylin" type compound, as compared with "Prontosil"—type compounds, containing the azo-linkage). Horlein was of the opinion that the results depended on an activation of the reticulo-endothelial system; but that Levaditi and Vaisman hold an opposite view, that of an inactivation or inhibition of streptococcal hemolysin, which theory is supported by the work of Osgood and Brownlee.²²

Long and Bliss¹⁷ showed that a 1 to 10,000 concentration of sulphanilamide in serum broth markedly inhibited the growth of streptococci, pneumococci (Types I and II), but had no effect on *Staph. aureus*, for example. Cohn⁵ showed that sulphanilamide in dilutions of 1 to 1000, to 1 to 100,000 exerted a bactericidal effect on gonococci *in vitro* when incubated 24 hours at 37.5° C. Levaditi and Vaisman¹⁶ showed that sulphonamide-azo dye derivatives protected mice against intraperitoneal injections of gonococci, which otherwise gave rise to fatal peritonitis and sepsis. Mellon, Gross and Cooper's²⁰ experiments, according to Orr, showed no indication that phagocytosis is a factor in the mechanism of the therapeutic action in gonorrhea. Bigler *et al.*,³ working with streptococci, concluded that the action of sulphanilamide seems to be independent of the leukocytes.

Summary. 1. Of 298 cases of gonorrheal urethritis in hospitalized males treated with sulphanilamide, 76% satisfied our criteria of cure.

2. In successful cases, the discharge and burning disappeared within 5 days of starting sulphanilamide, and the patients were discharged in 9 to 15 days after admission to the hospital.

* References can be found in Heterick's article.¹²

3. Of our acute cases, 73% were cured; of our chronic cases (over 28 days' duration), 83% were cured.

4. Sulphanilamide therapy in successful cases greatly reduces the time period for which medical treatment is necessary, as compared with the time generally necessary before the days of sulphanilamide.

5. Relatively few relapses after apparent cure with sulphanilamide have been reported in the literature, over follow-up periods generally less than 3 months.

6. We have used a relatively large and intensive method of dosage in our cases (all hospitalized), namely 120 grains a day for 2 days, followed by 60 grains a day for 3 days. We gave the drug at continuous 4-hour intervals, night and day. We now believe that 120 grains a day for 4 days, followed by 60 grains a day for 3 days, will prove to be more efficacious.

7. While severe and sometimes fatal toxic reactions doubtlessly occur, we have had only a few serious, and rarely a really dangerous reaction.

8. The drug is rapidly excreted. When administered in short intensive courses of not over 10 days, the danger to the blood forming system is probably slight. If continued over this time, even in smaller amounts a real danger of poisoning undoubtedly exists.

9. The presence of a complication seems to lessen greatly the chance of a rapid cure of the urethritis.

10. Local treatment would not seem to be warranted simultaneously with sulphanilamide.

11. A somewhat greater proportion of successes results among those who admit previous gonorrhea, than among those who deny it.

12. Inadequate dosage, administered prior to an adequate dosage and course of sulphanilamide, seems to impede the action of the drug.

13. The reason for the failure of the drug in about one-fourth of the cases is unknown, but certain seemingly pertinent inferences have been drawn.

14. We believe sulphanilamide has bettered the treatment of gonorrhea, but that older forms of therapy will continue to have a definite rôle.

15. The toxic reactions to the drug are characterized by pallor, cyanosis, malaise, anorexia, headache, occasionally vomiting, fever, and erythematous, macular rashes most noticeable over the face and extremities. The idiosyncrasy of patients plays a part in these reactions. These symptoms are similar to those noted in aniline poisoning. Excretion is rapid and recovery prompt when the drug is discontinued and fluids administered.

16. Adequate dosage should be maintained during treatment. To accomplish this, hospitalization is essential to assure this dosage and to protect the patient from untoward reactions.

Sharp and Dohme's, and Winthrop's Brands of sulphanilamide were used in this series.

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THE SEARCH FOR MORE EFFECTIVE MORPHINE-LIKE ALKALOIDS.*

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THIS investigation, begun in 1929, has proceeded under the auspices of the Drug Addiction Committee of the National Research Council at the University of Virginia, at the University of Michigan and recently at a number of clinical centers through the coöperation of the United States Public Health Service. Some 47 individuals are or have been directly concerned in carrying out the work.

In the beginning, two routes were open, either of which might lead to the solution of our problem, the production of a non-addicting analgesic. One of these was operation upon the alkaloids of promising structural type, especially those of the morphine group; the other was syntheses starting with unrelated or distantly related nuclei. The first path, while likely to lead to active drugs, had the disadvantage or attendant uncertainty of whether or not products derived from morphine greater than or comparable to it in analgesic power might be likewise addicting. The second route had the obvious disadvantage that the possible starting materials and the directions in which synthesis might be undertaken were multitudinous and there appeared to be no previous experience in this connection beyond isolated haphazard experiments. However, both paths have been followed assiduously and we will endeavor to describe some of the stations which have been passed along the way.

Coincident with the development of the analgesic effect of mor-

* Read by invitation at the joint session of the Federation of American Societies for Experimental Biology, at Baltimore, March 31, 1938.

phine there occur other, often medically undesirable, actions in the body, namely its respiratory, circulatory, gastro-intestinal, emetic, convulsant, and general depressant manifestations. We are obliged to speak of both the convulsant and general depressant actions of morphine because its effect is diphasic in all species though not equally so. An outstanding difference in the action of morphine in man and animals is the preponderance of convulsant action in many of the latter and of depression, especially of the respiratory mechanism, in the former. In addition, the administration of morphine to man, at least in many individuals, not only relieves the discomfort of pain and restlessness but also causes a pleasurable feeling of well-being, a "euphoria." Both the relief of discomfort and the euphoria may lead to repeated administration and repeated administration sooner or later leads to dependence, the *sine qua non* of addiction. Dependence is demonstrably physical as well as mental and it is our belief that there is a relationship between it and the chemical structure of the addicting agent of the morphine series just as probably as that there is a relation between chemical structure and the analgesic or any other property of the drug. The relationship, of course, may be either to the nuclear skeleton of morphine or to the presence of certain modifiable peripheral groups. We propose to show that modification of the latter may not uniformly modify the morphine picture which is presumptive evidence of a relation between the actions of morphine and the peripheral groups, and we submit that each successful demonstration of dissociation by chemical means between any of the properties of morphine adds to the hope of eventual dissociation of the analgesic and addicting factors.

The work itself on this project started and our description can also start most simply with the chemical modification exemplified in the naturally occurring alkaloid, codeine, which differs from morphine only in the presence of an OCH_3 group replacing a phenolic OH (Fig. 1). It is well known that codeine is weaker than morphine in analgesic, respiratory, depressant, emetic and intestinal effects. Clinical evidence indicates that it is less addicting than morphine, though there are no quantitative data available on the degree to which the addiction factor is reduced. On the other hand, in animals codeine has a much greater convulsant action and is more toxic.

If morphine is treated with reagents suited to replace the alcoholic hydroxyl by chlorine, such as phosphorus trichloride or thionyl chloride, isomeric chloromorphides are formed. Hydrolysis of either of these halogenomorphides with dilute acetic acid yields in varying amounts three isomers of morphine. Similarly we can prepare by halogenation and hydrolysis three isomers of codeine or these may be obtained by direct methylation of the morphine isomers.

The isomerism depends upon the position of the alcoholic hydroxyl, so that we have pairs of structural isomers of morphine and of codeine as the hydroxyl shifts from the 6- to the 8- carbon and pairs of diastereomers, whether the hydroxyl is on the 6- or the 8- carbon. Further, in each instance the alicyclic unsaturated linkage (between carbons 7 and 8 or between carbons 6 and 7) can be removed by controlled hydrogenation (Fig. 2). In this and the succeeding figures (Figs. 2 to 11) the structural formula of the parent substance (morphine in the present instance) is shown and, underneath, that portion only of the molecule is reproduced which has undergone the chemical change under consideration. In addition, in Figure 2 the isomeric configurations are indicated by reproduction of the portion of the molecule in which they occur. The substances thus represented (from left to right, upper row first)

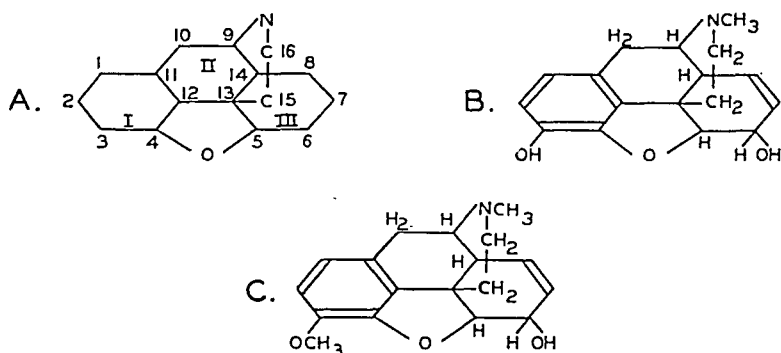


FIG. 1.—A, Morphine nucleus and numbering system. B, Morphine. C, Codeine.

are morphine, dihydromorphine, α -isomorphine, dihydro- α -isomorphine, β -isomorphine, dihydro- β -isomorphine, γ -isomorphine and dihydro- γ -isomorphine.* The isomeric configurations of codeine, dihydrocodeine and their isomers are identical and the codeine analogs in the order of the morphine series just enumerated are codeine, dihydrocodeine, isocodeine, dihydroisocodeine, allopseudocodeine, dihydroallopseudocodeine, pseudocodeine, and dihydropseudocodeine. We have then eight compounds, morphine, dihydromorphine and their isomers, differing from eight others, codeine, dihydrocodeine and their isomers, simply and only as morphine and codeine differ. If we compare these two groups serially we have an eightfold confirmation, or otherwise, of the typical difference exhibited in the change from morphine to codeine (Fig. 2).

The basis of comparison is the difference in effective doses expressed as a percentage of the greater dose. For example, the average fatal dose of morphine is 531, of codeine 241 mg. per kg., the difference is 290 or 54% of the greater dose. The toxicity of codeine

* All of the substances studied in this research were prepared at the University of Virginia by Lyndon F. Small, Erich Mosettig and their collaborators.

in relation to that of morphine then may be expressed as increased 54%. Again the respiratory minimal effective dose of morphine is 0.15, of codeine 1.30 mg. per kg. The difference is 1.15 or 88% of the greater dose, in this case the codeine dose, so that the respiratory effect of codeine in relation to that of morphine may be expressed as decreased 88%. In other words, where the line extends upward on the + side of the zero abscissa the codeine or derivative member of the pair is the more effective; where it extends downward the derivative member is the less effective, and the length of the line is related to the degree of difference. This explanation of the method of comparison applies also to Figures 3 to 11.

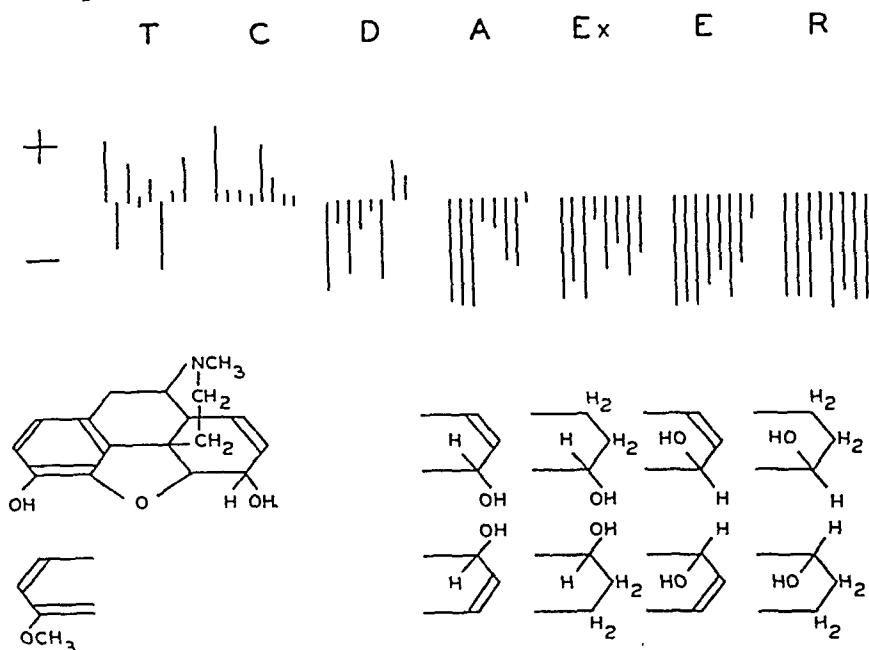


FIG. 2.—Comparison of morphine, dihydromorphine and their isomers with codeine, dihydrocodeine and their isomers; the effect of methylation of the phenolic hydroxyl. The initials at the top of the 7 columns indicate: toxicity (*T*), convulsant (*C*), general depressant (*D*), analgesic (*A*), exciting (*Ex*), emetic (*E*) and respiratory (*R*) effects. Each vertical line indicates the relationship in a single pair and the order is the same for each effect—morphine-codeine first, dihydromorphine-dihydrocodeine second, α-isomorphine-isocodeine third, and so on.

In this series of morphine and codeine isomers then the codeine-like difference is well borne out, toxicity and convulsant action are usually increased, other effects are decreased by methylation of the phenolic hydroxyl. The same result is obtained if we methylate similarly other morphine derivatives, the alcoholic ethers and esters and the desoxymorphines, for example. Methylation of the halogenomorphides, however, decreases toxicity and convulsant action as well as the other effects (Fig. 3).

To determine whether we are dealing with an effect of inactivation of the phenolic hydroxyl or of the addition of a methyl group

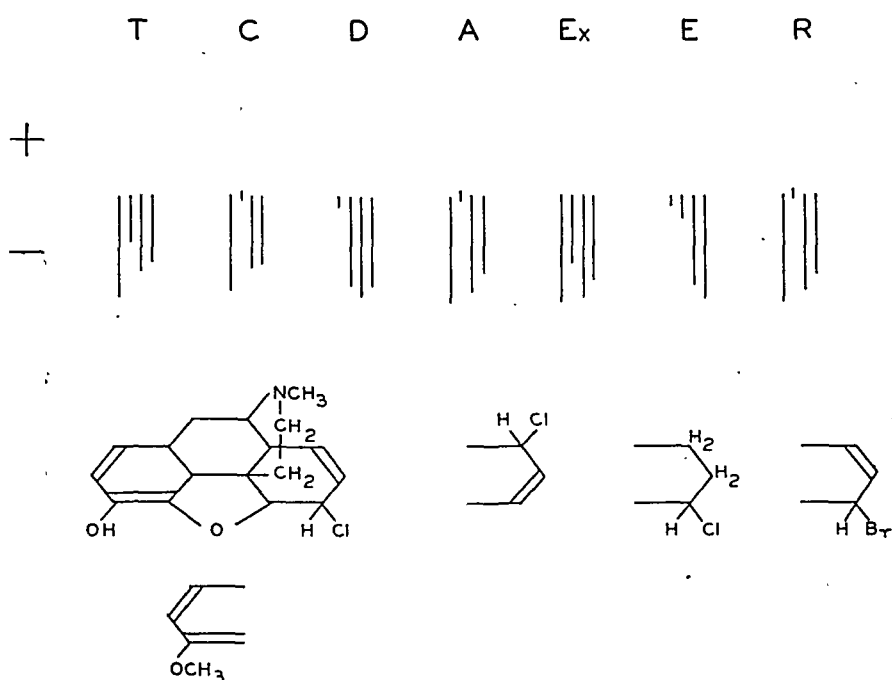


FIG. 3.—The effect of methylation of the phenolic hydroxyl of α -chloromorphine β -chloromorphine, dihydrochloromorphine and bromomorphine.

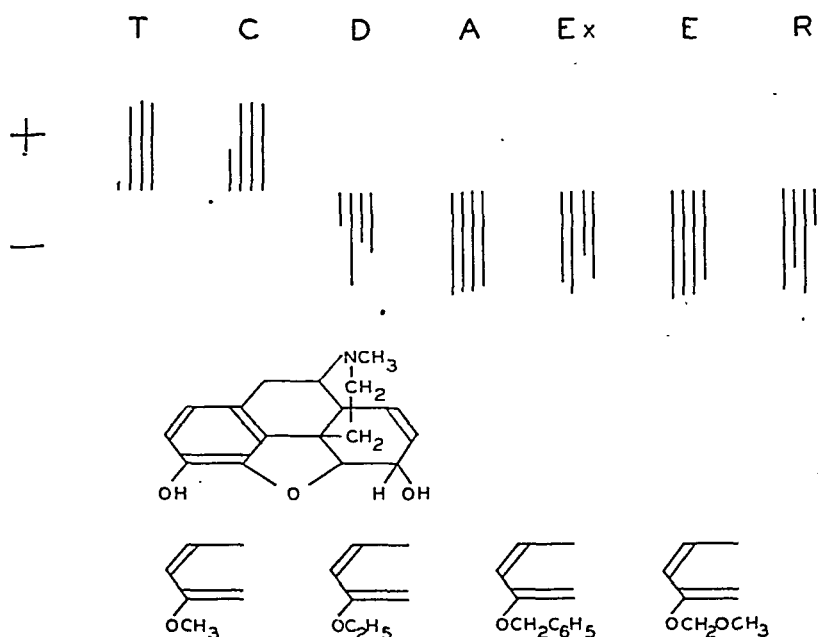


FIG. 4.—The effect of muzzling the phenolic hydroxyl of morphine and dihydro-morphine with different groups—methyl-, ethyl-, benzyl-, and methoxymethyl-.

the phenolic hydroxyl can be muzzled by other groups in morphine and some of its derivatives. In Figure 4 the first line under toxicity, convulsant action, and so on, represents the difference in effect brought about by methylation of morphine and dihydromorphine, the second line the difference when the muzzling group is ethyl, the third line the difference when the muzzling group is benzyl and the fourth when the muzzling group is methoxymethyl. The latter two groups were selected because of a difference in the ease with which they are removable by hydrolysis. There are some details suggestive of specific differences, but in the main the four muzzling groups have the same effect. In the main also this change has been

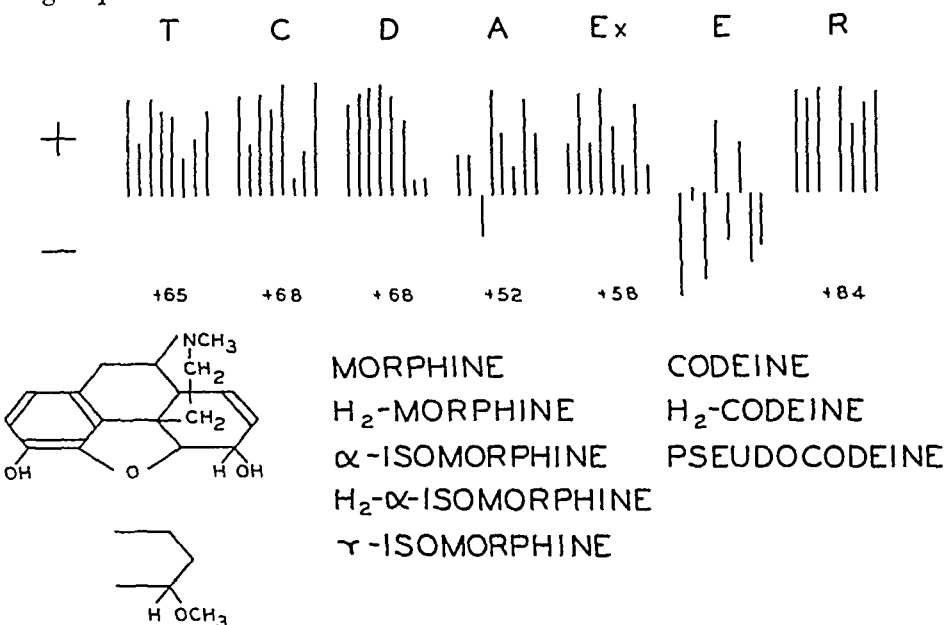
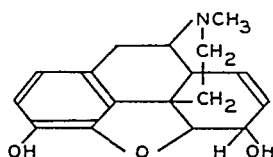
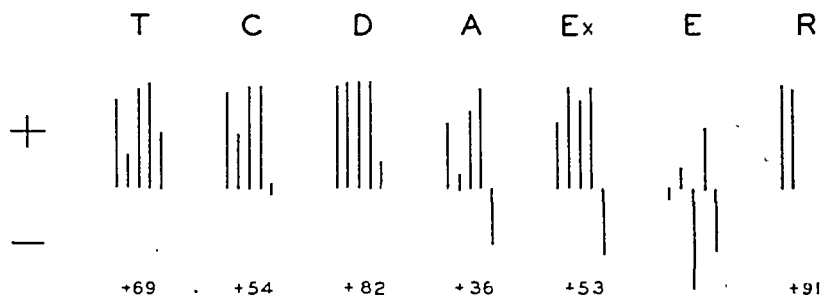


FIG. 5.—The effect of methylation of the alcoholic hydroxyl of the substances listed. Each figure below the graph is the composite percentage difference in effect for the group compared.

disadvantageous because even though we may show a reduction in addiction liability in the codeine analogs; that is, in the muzzled compounds, the reduction in other effects is too great for practical usefulness.

Another indication of the non-specificity of the addition of a methyl group can be derived from its use to muzzle the alcoholic hydroxyl of morphine and its derivatives (Fig. 5). Here the picture is quite different—effectiveness in most instances, including toxicity, is definitely increased. There are two points worthy of particular mention because of their bearing on our general thesis, namely, the variable change in emetic action whatever the effect in other respects, and the quantitative difference in analgesia and respiratory effect. The former is increased less (52%), the latter to a significantly greater extent (84%) than the change in toxicity (65%).

Many other changes have been effected in the alcoholic hydroxyl. Ethyl substitution (Fig. 6) gives a result very like that of methyl substitution, qualitatively and quantitatively. Note again the variable change in emetic effect and the quantitative difference in analgesia (average increase 38%), respiratory effect (average increase 91%) and toxicity (average increase 69%). The results of acetyl substitution (Fig. 7) are more irregular, possibly because of the ease with which the acetyl group may be removed by hydrolysis. Changing the hydroxyl to a ketone (Fig. 8) has an effect like that of alkylation. The same can be said of removal of the hydroxyl



MORPHINE

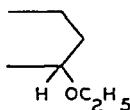
 H_2 -MORPHINE α -ISOMORPHINE $H_2\alpha$ -ISOMORPHINE γ -ISOMORPHINE

FIG. 6.—The effect of ethyl substitution of the alcoholic hydroxyl of the substances listed.

and its substitution by hydrogen (Fig. 9). This last change produces the greatest and most uniform increase in both depressant and analgesic effects though it also tends to shorten the duration of action. Halogenation, on the other hand (Fig. 10), is irregular in its effect, increasing the useful properties other than depressant action relatively little.

In sharp contrast to all of these modifications of the alcoholic hydroxyl is the effect of its replacement by a basic group (Fig. 11). These groups were tried because of the results obtained with simple phenanthrene amino alcohols, and it is disappointing to find that toxicity and all morphine-like effects are decreased markedly whether the basic group is diethylamino- or piperidino-.

A different type of morphine derivative is produced by the addition of a new nuclear substituent (Fig. 12). For example, in 2-aminomorphine a basic amino group has been introduced at carbon

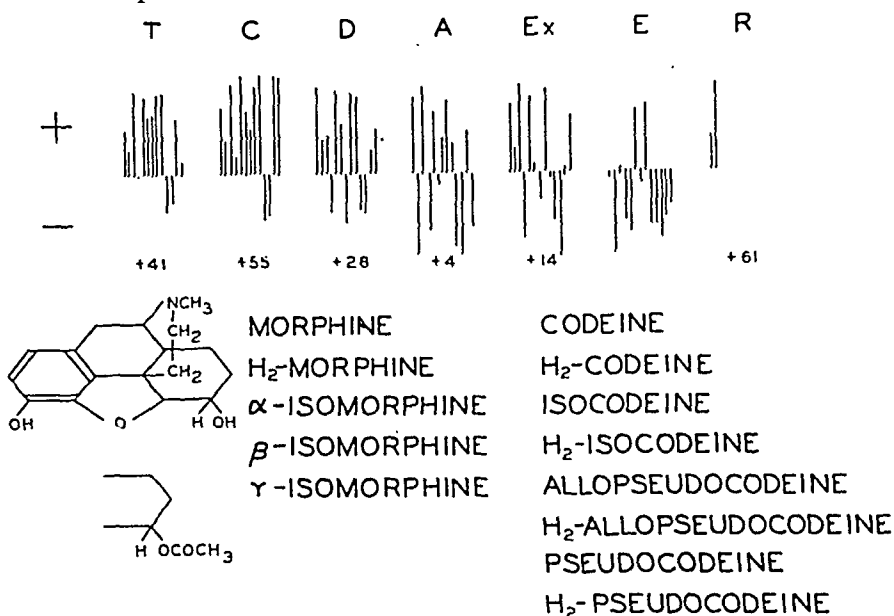


FIG. 7.—The effect of acetyl substitution of the alcoholic hydroxyl of the substances listed.

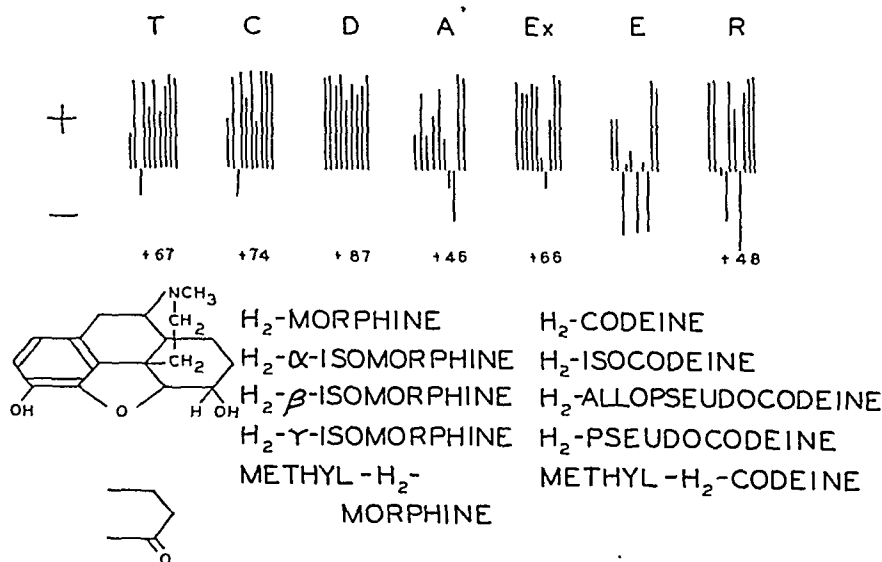


FIG. 8.—The effect of changing the alcoholic hydroxyl to a ketone in the substances listed.

-2 and in the hydroxycodines and hydroxycodionones a hydroxyl group at carbon -14. In each of these instances the morphine-like properties are decreased in the new compounds.

Recently nuclear substitution has been accomplished also in the alicyclic ring of the morphine molecule either at carbon -7 or carbon -5. This group of derivatives and the method of preparation are

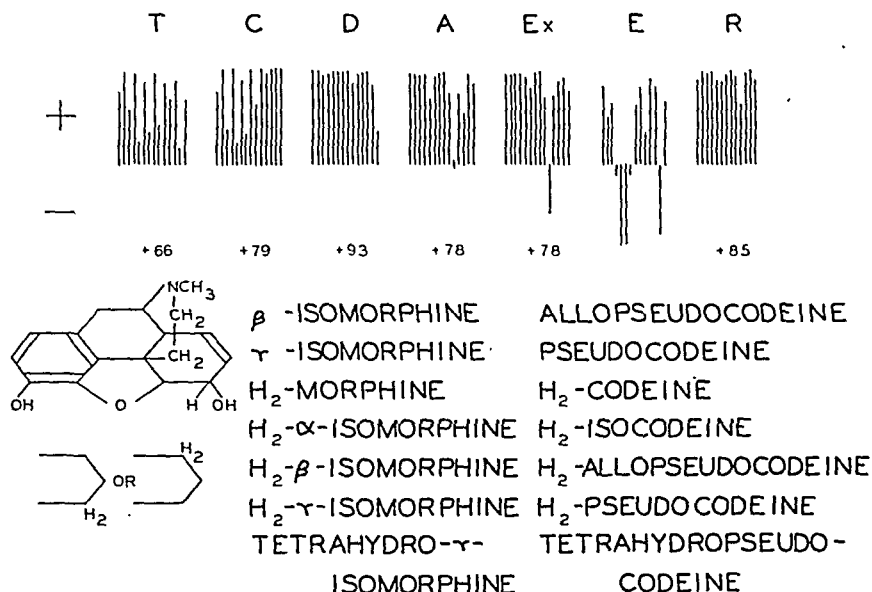


FIG. 9.—The effect of removal of the alcoholic hydroxyl and its replacement by hydrogen in the substances listed.

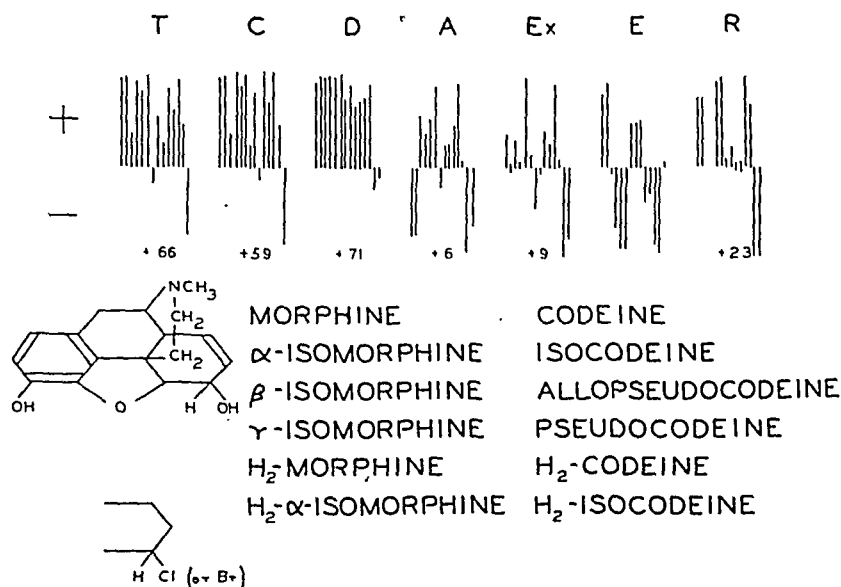


FIG. 10.—The effect of replacement of the alcoholic hydroxyl of the substances listed by chlorine or bromine.

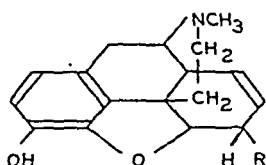
entirely new. Thebaine, the naturally occurring alkaloid which is practically a waste product of morphine manufacture, is the start-

ing material and through a series of steps an alkyl derivative of morphine or codeine or any of their derivatives is possible. Examples are methyldihydromorphine and methyldihydrocodeine both of which are not convulsant, are less toxic and generally less effective than dihydromorphine and dihydrocodeine, respectively.

T C D A Ex E R

+

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MORPHINE

H₂-MORPHINE

β-ISOMORPHINE

ALLOPSEUDOCODEINE

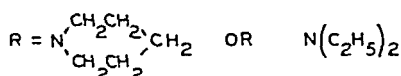


FIG. 11.—The effect of replacement of the alcoholic hydroxyl by a basic group—piperidino- or diethylamino—

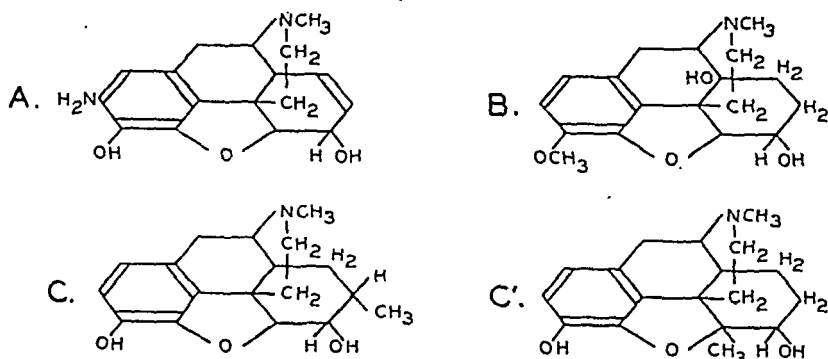
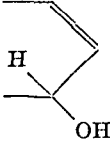
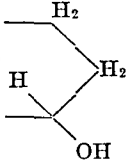
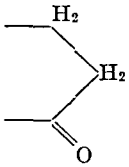
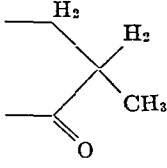
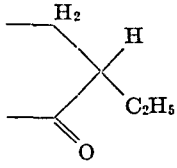
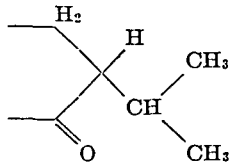
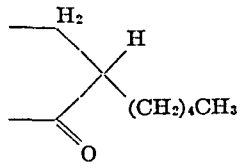


FIG. 12.—Examples of nuclear substitutions: A, 2-Aminomorphine. B, Dihydrohydroxycodeine. C, C', Methyldihydromorphine. (Either configuration is possible).

The alkyl derivatives of this type of dihydromorphinone constitute a very interesting series. Of these methyldihydromorphinone is most promising and is being subjected to clinical trial. In man, it is twice as effective as an analgesic with a duration of action

TABLE 1.—MINIMAL EFFECTIVE DOSES IN ANIMALS.

	Modification from morphine molecule.	Toxicity.	Convulsant.	Depressant.	Analgesic.	Exciting.	Emetic.	Respiratory.
Morphine		531	531	6.75	0.75	0.57	0.22	0.15
Dihydromorphine		133	133	17.70	0.26	1.77	0.17	0.11
Dihydromorphinone		84	67	1.77	0.17	0.17	0.08	0.011
Methyldihydromorphinone		25	25	3.00	0.07	0.10	0.07	0.012
Ethyldihydromorphinone		27	22	2.01	0.17	0.09	0.17	0.021
Isopropyldihydromorphinone		17	13	2.25	1.33	0.26	1.80	0.10
Amyldihydromorphinone		11	5	0.22	0.36	0.04	0.36	0.002

approximately as great as morphine. No emetic action has appeared and no sign of respiratory depression in a large series of cases. In substitution studies in human addicts it has a very brief duration of dependence satisfaction possibly suggestive of a low addiction liability. The work with this substance in man is being extended in order to determine definitely its safety in respect to tolerance and addiction.

Before we leave this group note the quantitative and directional differences which have developed (Table 1). The figures in the table are minimal effective doses in animals and they present some very excellent examples of dissociation of morphine-like properties. Note, for example, that dihydromorphinone is more effective than dihydromorphine all the way along the line, while methyldihydromorphinone is more effective in respect to analgesia and excitement, not materially different in respiratory effect, but definitely less depressant. With isopropyldihydromorphinone in comparison with dihydromorphinone there is a marked difference in the change in analgesic and exciting effects—the former decreased from 0.17 to 1.33 mg. per kg., the latter only from 0.17 to 0.26 mg. per kg. In addition, the respiratory effect of the isopropyl derivative shows a tenfold decrease, from 0.011 to 0.10 mg. per kg. while depressant action is decreased only from 1.77 to 2.25 mg. per kg. Note also that analgesic and exciting actions are modified strikingly in opposite directions in amyldihydromorphinone—the former is decreased from 0.17 to 0.36 mg. per kg., and the latter is increased from 0.17 to 0.04 mg. per kg. Amyldihydromorphinone is the most toxic member of the group and is very markedly depressant to respiratory activity. It is also noteworthy that it is the only substance in this series, the depressant dose of which is less than that for analgesia.

In respect to the other possible route toward our goal, there are two important considerations. First, if the morphine picture is dependent upon the peripheral groups of the morphine molecule and the phenanthrene nucleus is just a carrier for these groups, then starting with phenanthrene it would seem possible by addition of suitable groups to bring out features of the morphine picture and we hope the analgesic feature to the greatest degree. On the other hand, if the morphine picture is inherent in the phenanthrene nucleus and the outlying groups are only handles or keys permitting its development, then the sort of analgesic that we want free from addiction liability will not be found in a phenanthrene derivative and we must rather try to build up a compound with a different nuclear structure. Having in mind both of these considerations our synthetic route has become a number of parallel roads along which

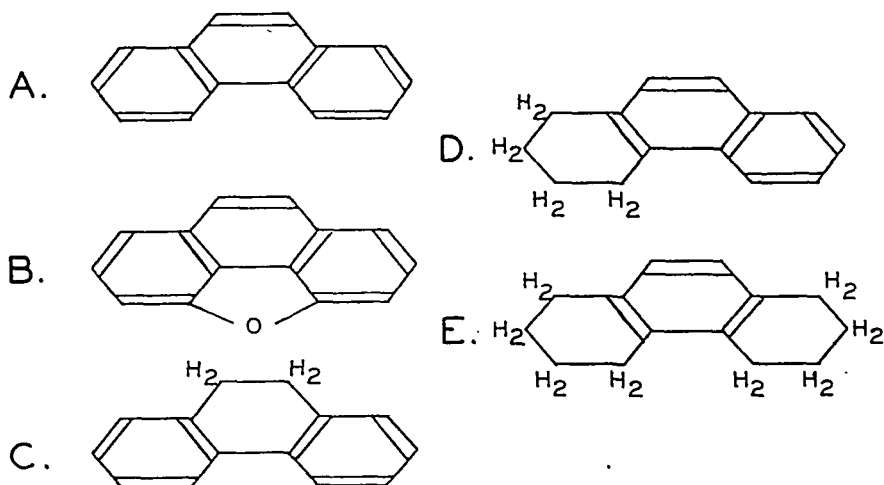


FIG. 13.—*A*, Phenanthrene; *B*, phenanthrylene oxide; *C*, 9, 10-dihydrophenanthrene; *D*, 1, 2, 3, 4-tetrahydrophenanthrene; *E*, 1, 2, 3, 4, 5, 6, 7, 8-octahydrophenanthrene.

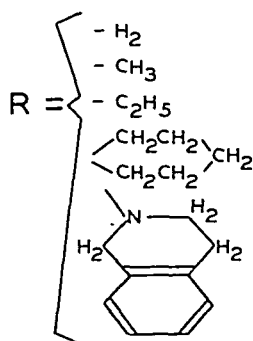
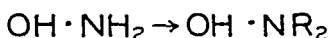
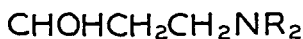
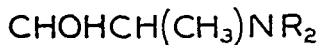
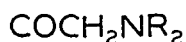
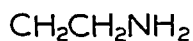
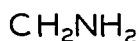
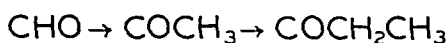
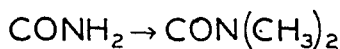
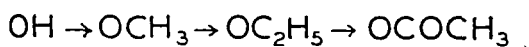


FIG. 14.—Some of the substituents which have been added to phenanthrene and to a lesser extent to the other nuclei of Fig. 13.

we progress as rapidly as the difficulties of syntheses will permit. The phenanthrene road itself has a number of parallel lanes according to whether the starting material is phenanthrene, a partially hydrogenated phenanthrene or phenanthrylene oxide. Figure 13

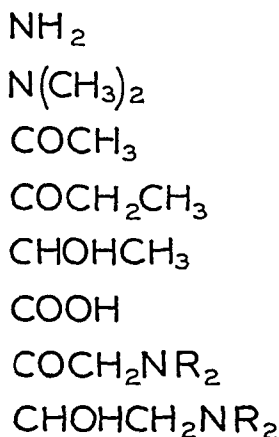
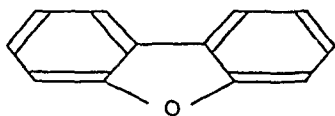


Fig. 15.—Dibenzofuran and some of the substituents which have been added to it.

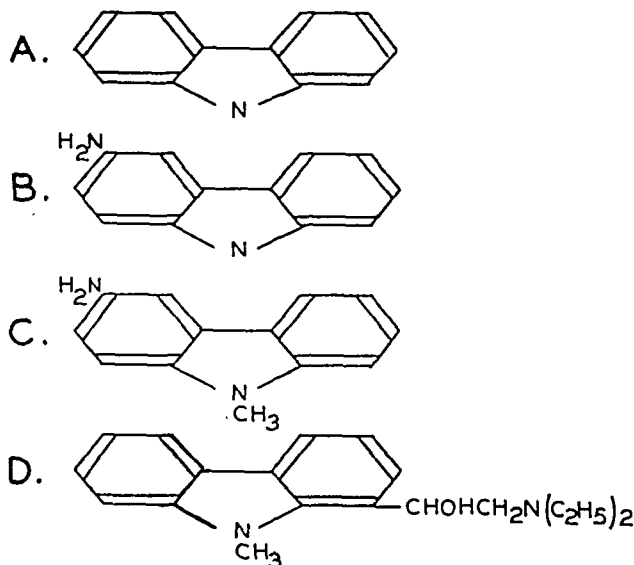


Fig. 16.—A, Carbazole; B, 3-aminocarbazole; C, 3-amino-9-methylcarbazole; D, 9-methyl-2-[1-hydroxy-3-diethylamino]propyl carbazole.

shows these simple nuclei and Figure 14 some of the substituents which have been added to phenanthrene and to a lesser extent to hydrogenated phenanthrenes and phenanthrylene oxide.

The two other most important highways which have been travelled so far start from dibenzofuran and carbazol. The former differs from phenanthrene in having only two 6-carbon rings but it has an oxygen bridge as in phenanthrylene oxide. Carbazol is similar to dibenzofuran in having only two 6-carbon rings; it has a third ring closed by a nitrogen bridge. Figure 15 shows a few of the substituents which have been added to dibenzofuran, and Figure 16, carbazol and some of its derivatives. From examination of nearly 200 compounds synthesized for this phase of the work, most of them new, certain conclusions can be drawn.

Of the simple nuclei without substituents phenanthrene, octahydrophenanthrene, dibenzofuran and carbazol are nearly inert. 9, 10-Dihydrophenanthrene and tetrahydrophenanthrene are more effective, that is, more depressant when administered to animals. Derivatives of 9, 10-dihydrophenanthrene, however, are highly emetic and often convulsant. The addition of simple substituents to the nuclei increases their effectiveness and may even cause the appearance of some analgesic action. Increasing the length and complexity of the side chain up to a certain extent at least increases activity. It seems especially desirable to have a tertiary nitrogen in the side chain and a hydroxyl group attached to the nucleus or in the side chain. Of analogous dibenzofuran and phenanthrene derivatives the former are the more analgesic but also the more toxic.

The most effectively analgesic phenanthrene derivative that we have found so far is one derived from tetrahydrophenanthrene with a hydroxyl attached to the nucleus together with a tetrahydroisoquinoline group (Fig. 17). It is definitely analgesic and depressant in cats with a dose as small as 15 mg. per kg. but has not developed other typical morphine-like actions. Its homolog (Fig. 18) in which a CH_2 intervenes between the phenanthrene and tetrahydroisoquinoline is not more analgesic but even in small dose produces typical morphine-like excitement in cats. It also dilates the pupils and increases the heart rate, but is not convulsant and only very slightly emetic. The isomer of this homolog in which the side chain is on carbon -2 is inactive.

The carbazol derivatives are probably the most promising of our synthetic substances exhibiting a high degree of analgesic and depressant effects with low toxicity and usually little emetic action. The most active member is an amino alcohol derivative (Fig. 16, *D*), the effective dose of which is only 10 mg. per kg. It is not morphine-

like in other respects. The carbazols in general lower the temperature and are apt to produce considerable incoördination, besides being occasionally emetic. If we can find the means of avoiding these side actions and effect a little greater increase in analgesic action this group offers considerable hope of a useful clinical substance for which there is no reason to anticipate addiction liability.

In conclusion, very brief reference should be made to the clinical studies which are going forward in connection with this work.

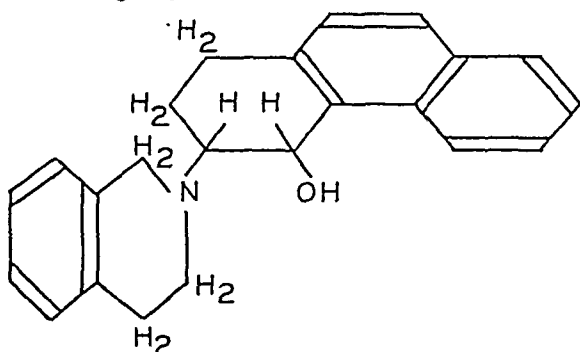


FIG. 17.—3-py-Tetrahydroisoquinolino-4-hydroxy-1, 2, 3, 4-tetrahydrophenanthrene.

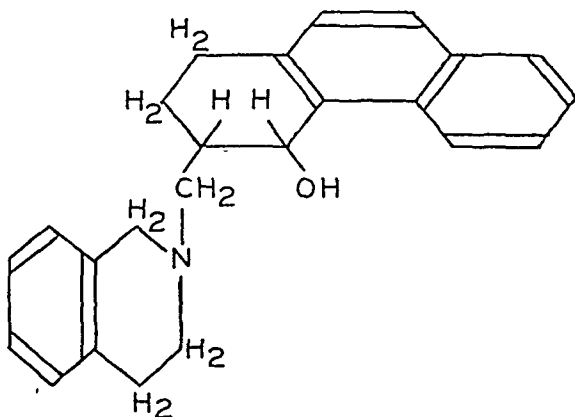


FIG. 18.—3-[(Tetrahydroisoquinolino)-methyl]-4-hydroxy-1, 2, 3, 4-tetrahydrophenanthrene.

Clinical facilities have been made available at a number of places in order that the pharmacologic studies may be extended to man. These facilities will permit the determination of effectiveness for clinical relief of pain and cough, the existence or otherwise of side effects, the effect of prolonged administration to non-addicts and the effect of selected substances on morphine addicts particularly in terms of dependence satisfaction. A score of substances have so far been submitted to some degree of clinical trial and of these the most promising is methyl dihydromorphinone.

MASSIVE DOSE ARSENOTHERAPY OF SYPHILIS BY THE INTRAVENOUS DRIP METHOD: FIVE-YEAR OBSERVATIONS.*

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THE method of the slow intravenous drip has made possible the safe introduction of drugs in amounts far exceeding our previous conception of dosage.^{3,4a} The chemotherapy of early syphilis offered a clinical proving ground for the testing of this basic therapeutic principle. The technique of the intravenous drip and the preparation of solutions and materials have been the subjects of previous communications.^{4b,5} The application of the drip method to the therapy of early syphilis has made possible the safe introduction of arsphenamine in doses sufficiently great to approach the "sterilisatio magna" of Ehrlich.²

Clinical Material and Dosage. In a previous paper, 25 otherwise healthy male patients, suffering from primary or early secondary syphilis, were treated with massive doses of neoarsphenamine by the intravenous drip method. The immediate and specific effects on the luetic lesion, the immediate toxic effects, particularly the fevers, toxicodermia and polyneuritis were described.¹ A total approximating 100 gm. of neoarsphenamine was given over a span of time that averaged less than 5 days. The smallest amount of neoarsphenamine injected was 2.4 gm.; the largest amount 5 gm.; and the average dose 4 gm. The majority of patients were treated over the course of 4 days, the longest duration of time was 6 days.

Late Toxic Sequelæ. None of the late parenchymatous lesions that may follow the exhibition of the heavy metals was experienced in any of the patients. Neither was there any evidence of jaundice, or liver damage, or any of the serious exfoliative skin lesions.

* This report is No. VI in the *Studies of Velocity and the Response to Intravenous Injections*, and emanates from the Department of Medicine, Service of Dr. George Baehr; Department of Dermatology, Service of Dr. Isadore Rosen; the Mount Sinai Hospital, and the Division of Venereal Disease, Department of Health, New York City.

Clinical Course. The clinical course of our patients during the 5 years that have elapsed since therapy was begun has been exceedingly difficult to follow. It has seemed wisest to present the data rather than statistics or conclusions. Five patients (Cases 5, 6, 10, 13, and 24) disappeared from observation before they achieved seronegativity. Two of these disappeared before 1 month had elapsed, 1 before the second month, 1 before the third month, and 1 before the fifth month of observation. The last named (Case 6) unfortunately, received only 2.9 gm. of neoarsphenamine, an amount which we now believe to be insufficient in the massive treatment of early syphilis.

A second group of 5 patients (Cases 9, 12, 15, 16, and 21) achieved seronegativity, but were not followed a sufficient length of time for satisfactory observation. In particular, 1 of these patients (Case 15) maintained a 4+ Wassermann for 11 months and had only 1 negative Wassermann at the end of the twelfth month, though he received the full course of 5 gm. of neoarsphenamine. Of the others in this group, 2 disappeared from observation in the second month, 1 in the fourth month, and 1 in the eighth month.

Of the remaining 15 patients, we have repeated negative blood Wassermann tests in 11, sufficient for us to feel certain that their late clinical course has been wholly and completely uneventful. No one of these patients received any other therapy of any nature whatsoever during this time. We have spinal fluid findings on 13 of the group: 5 made at the end of a year, 1 at the end of 2 years, and the remaining 7 made at the end of 5 years—all of which are completely negative so far as serology, cell count and globulin reactions are concerned, with the possible single exception to be detailed later. There are 9 normal teleoroentgenograms in this same group, one made at the end of 4, and the others at the end of 5 years of observation.

Four patients in this group require explanatory notes: One man (Case 25) who was 4+ on admission and at the end of the first month of observation, was not seen again for $4\frac{1}{2}$ years, at the end of which time he had a negative blood Wassermann, negative spinal fluid, and a normal teleoroentgenogram. A second member of this group (Case 22) disappeared from our observation when he was discharged from the hospital and was not seen by us until 54 months had elapsed, at which time his Wassermann, spinal fluid, and teleoroentgenogram were normal. This patient, a hospital orderly, continued the therapy of his case without our supervision. He reports that his Wassermann was negative 6 months after discharge from the hospital, by which time he had already received 12 injections of mercury. Because of his knowledge of the disease he insisted upon receiving therapy wherever he went and, to date, he has received another 27 injections of mercury. He had repeated Wassermann tests done at various institutions including Welfare Island, the

Hospital for Joint Diseases, and the New York Hospital. On one occasion, in 1935, his blood Wassermann and spinal fluid were simultaneously reported to be 2+, both tests being done at the same time. Thereafter, however, and at all of the other institutions his Wassermann and spinal fluid have been persistently negative, the succeeding spinal fluids being done 3 months and 3 years respectively after the one reported positive. Whether this one blot on his escutcheon represents a true recrudescence or a technical error, cannot be stated but it is only fair to point out that it would be exceedingly unusual for a recrudescence to be so transitory.

CHART 1.—CLINICAL DATA.

Case number.	Initials.	Hospital number.	Primary lesion.	Dark-field examination.	Secondary eruption.	Miscellaneous.	Date of admission, 1933.	Duration of treatment in days.	Total neoarsphenamine injected in grams.
1	D. M.	352,575	○	○	+	May	4	2.4
2	W. S.	352,817	+	○	+	Iridocyclitis	June	4	2.9
3	G. S.	357,027	+	○	+	June	4	3.5
4	L. S.	353,445	+	+	○	Primary of lip	June	4	3.3
5	W. C.	353,639	+	+	○	June	4½	3.2
6	O. S.	353,819	+	+	○	June	4	2.9
7	J. S.	372,747	+	+	○	July	5	4.0
8	J. C.	369,104	○	○	+	July	5	4.6
9	A. S.	355,089	+	+	○	Primary of lip	July	5	4.7
10	J. D.	355,194	+	+	+	July	5	4.8
11	W. C.	355,327	+	+	○	July	5	4.7
12	E. O.	355,435	+	+	+	Primary of lip	July	5	4.8
13	A. F.	355,549	○	○	+	July	6	4.5
14	C. R.	366,635	+	○	+	August	4	3.6
15	H. L.	355,830	+	○	○	August	4	5.0
16	L. T.	355,956	+	+	+	August	4	4.45
17	J. B.	376,333	+	+	○	August	5	4.4
18	E. R.	368,574	+	○	○	Sept.	4	3.9
19	G. C.	357,027	+	○	+	Sept.	5	4.5
20	R. R.	357,342	+	○	+	Sept.	4½	3.4
21	S. S.	357,509	+	○	+	Sept.	5	4.5
22	H. B.	357,890	○	○	+	Sept.	5½	4.2
23	B. S.	357,740	+	○	+	Primary of lip	October	6	4.0
24	J. K.	358,034	+	○	+	October	6	2.8
25	T. H.	358,321	+	○	○	October	5	4.3

Two patients succeeded in reinfecting themselves with syphilis. In the 1 instance, the evidence is beyond doubt; in the other, highly presumptive. The first of these (Case 3) was admitted to our Service in June, 1933, with primary and secondary lesions. The dark field was positive. His Wassermann was 4+. Over the course of 4 days he received 3.5 gm. of neoarsphenamine. At the end of the second month of observation his Wassermann was \pm ; at the end of the 3rd, 4th, 8th, and 18th months, negative. He returned 38 months after the first infection and 18 months after the last negative Wassermann, with a sore on his penis that had been present for 3 days. He admitted frequent exposure. The primary infection in 1933 had been at the urethral meatus. The new lesion was in the coronal sulcus near the base, and was quite indurated. Firm, enlarged lymph nodes were present in the groin. The dark-field examination from the new sore showed many typical *Spirocheta pallida*. His

CHART 2.—WASSERMANN REACTION.

[illegible]

blood Wassermann was still negative. Treatment was deliberately withheld, and 3 days later the dark-field examination was still positive. Two days later a macular lesion appeared on the trunk, the left epitrochlear gland became enlarged, the primary sore was now chancroidal, and smears showed the Ducrey bacillus. Nineteen days after the first appearance of the patient, the macular eruption was still visible and the blood Wassermann test was 4+. Treatment was deliberately withheld until all of the data of reinfection could be obtained. He was now given bismuth intramuscularly and arsphenamine intravenously. He has been under treatment to date for 18 months by the conventional methods. His Wassermann is still positive, as contrasted to Wassermann negativity obtained in 3 months by the massive dose therapy. During the course of the second treatment there were no unusual toxic or allergic reactions, demonstrating that the patient had not been sensitized to arsenic by the massive dosage.

In the other patient (Case 8), the evidence that reinfection also occurred is presumptive, but not completely proven. He was first admitted with secondary syphilis and a 4+ Wassermann. Originally, he was given 4.6 gm. of neoarsphenamine over the course of 5 days. At the end of 2 months his Wassermann was negative and he had negative Wassermans at the 3d, 7th, 9th, 12th, and 19th months of observation. His last Wassermann was performed on February 14, 1935, at which time he was clinically well. This patient was a profound alcoholic and indulged in frequent and promiscuous sexual relationship. One week prior to his last Wassermann he had had repeated sexual exposure, and 3 genital sores appeared immediately after his last visit, or 1 week following the last sexual exposure. One of the sores was at the site of the previous lesion, one was in the sulcus, and the third was on the glans penis. He had been treating the lesions himself with carbolic ointment and aristol powder for the 4 weeks that ensued between the visits. Two dark-field examinations were negative. Blood Wassermann test was 4+. The lesions assumed a chancroidal character and showed a tendency to heal; a month later they were virtually healed. There was no eruption. The right inguinal nodes were aspirated, but no *Spirocheta pallida* could be demonstrated. The coronal ulcer was aspirated and this was similarly negative. Treatment had been deliberately withheld. However, the patient went to a private physician who immediately instituted therapy. The critical reader may form his own conclusion as to whether this was a recrudescence of the original infection, a superinfection, or a reinfection.

Comment. It would be hazardous and unsafe to draw conclusions or calculate percentages on a series of cases so small and on observations that are so imperfect. One claim, however, seems completely justified. This would hold that primary and early secondary

syphilis may not only be "cured" by the massive injection of neoarsphenamine, by the method we have described, but that a permanent and complete result is possible though no other therapy is introduced in any way or at any time.

If primary and early secondary syphilis can be cured and remain cured as the result of 4 or 5 days of intensive treatment, a means for the successful eradication of this dread disease is at hand. The possibilities present a new vision of the syphilis problem for public health officials and legislators. If the further work corroborates our findings that the method is free from excessive hazards, beyond the expectancy in any of the usual forms of arsenotherapy and that, under scrupulously controlled technique, the method may be applied to the routine treatment of syphilis, the significance of these observations to the patient as an individual and to the community as a whole, both in the public health aspects and in the economics of chronic disease, can scarcely be overstated or overemphasized. At the present time, however, the method must be considered experimental and should not be practiced in the routine treatment of syphilis until there has accumulated a much greater experience than we have reported. Should our experiences and findings be confirmed, there will have been accomplished the chemotherapeutic goal that Ehrlich sought—"sterilisatio magna."

The original work on this problem was made possible through the generosity of the late Ernst Rosenfeld.

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FOUR PHYSIOTHERAPEUTIC DEVICES FOR THE TREATMENT OF PERIPHERAL VASCULAR DISORDERS.

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THE purpose of this presentation is to describe four physiotherapeutic devices for the treatment of peripheral vascular disease. They have been used successfully at this hospital for periods of from 1 to 4 years.

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Three of these devices were constructed by one of us (H. M.) to carry out forms of therapy already well known, namely, controlled heating, alternate suction and pressure, and iontophoresis. The advantage over apparatus previously described lies solely in their simplicity, portability, and small expense. These factors have permitted us to construct many units, to treat a much larger number of patients, and to shorten the duration of hospitalization by supplying apparatus for patients to take home with them.

The fourth device (designed by I. S.), is a bed altered to permit the patient to rest with his legs dependent. Its purpose is to increase the hydrostatic factor of the blood pressure in the leg arteries, and so to improve the circulation through partly occluded vessels. A thermo-regulated cradle is built into it. This bed has proved especially useful in treating patients with rest pain so great that the horizontal position of the leg could not be tolerated.

Besides the details of construction, a brief review of the literature and directions for using the apparatus will be given.

A Simple Thermoregulator for Maintaining Optimum Temperature in a Foot Cradle. Starr¹⁵ and Severinghaus¹⁴ have described thermoregulated cradles, and these devices have been used for a sufficient time to prove that they will relieve pain in many cases of peripheral vascular disease. A number of types are on the market. The cheapest of which we have knowledge sells for \$50.

A simplified form of such apparatus is shown in Figure 1. The letters show the parts mentioned in the text. To construct it one needs:

1. One 60-watt electric light bulb (A, Fig. 1).
2. One electric light socket and switch, cord, and plug for connection with house current.
3. A simple adjustable thermostat with thermometer* (B, Fig. 1).
4. A piece of $\frac{1}{32}$ inch hard black vulcanized fiber sheet, 12 by 16 inches.†
5. One piece of copper sheeting, $\frac{1}{32}$ inch thick, 1 inch by 6 inches.
6. Board for mounting approximately 17 inches by $3\frac{1}{2}$ inches, by $\frac{1}{4}$ inch. The total cost of materials is approximately \$10.

This apparatus is mounted on the board, the copper sheet being bent to support the light socket. Two layers of fiber sheet are bent around the light bulb, as shown. The inner layer must be at least $\frac{1}{2}$ inch from the bulb at the nearest point. The outer layer is fastened upon the inner layer at the mounting board, but extends 1

* We use a device manufactured for regulating the heat of houses; a United Electric Controls Company (69 A St., Boston) No. 11 Thermostat. For a slight additional cost the manufacturer has altered the range to meet our requirements, 80° to 105° F. We have obtained this thermostat, so altered, from the Pennsylvania Distributing Company, 2401 Chestnut St., Philadelphia, Pa., at a cost of about \$8.50. The order should specify "without outlet box" as the latter, usually sold with the thermoregulator, is not needed.

† Obtainable from the Wilmington Fibre Specialty Company, Wilmington, Del.

inch beyond the inner layer at the greatest distance from the mounting board. Anyone assembling this apparatus must absolutely assure himself that the patient's foot cannot come in contact with either the bulb or the inner layer of the guard.

This apparatus is hung inside any leg cradle with the lamp end up. The thermostat is adjusted, usually by the patient himself, until a maximum of comfort is obtained. In our experience, the temperature selected is usually between 85 and 95° F. The feet of hospital patients are maintained at this temperature constantly whenever they are in bed. If they must leave the hospital before pain is gone or lesions completely healed, they take a thermoregulator home with them and use it until all acute symptoms have subsided.

These thermoregulators have also been employed in the treatment of certain patients with reduced circulation to the feet but without either rest, pain or acute lesions. A number of intelligent elderly arteriosclerotic patients, who complained chiefly of cold feet, have received great comfort by using a thermoregulated cradle at night during the winter months. As the incidence of acute lesions in peripheral vascular disease is much greater in winter than in summer, one has the right to expect that maintaining the temperature of the feet in such cases may prevent the development of lesions. It is hoped that the greater availability due to lessened expense may make possible a more exact study of this subject.

Simple Apparatus for the Application of Alternate Suction and Pressure to the Fingers. Alternate suction and pressure for the treatment of peripheral vascular disease has been studied and advocated by Landis and Gibbon,^{8a,b} by Reid and Herrmann,¹² and by Herrmann and Reid.⁵ Occasionally the digital arteries are mainly involved, and the outstanding complaint is of an indolent lesion localized to a digit. Symptomatic relief can often be obtained by frequent application of suction and pressure to this most affected part. The simple apparatus to be described was designed to apply alternate suction and pressure to any finger. It can be used by the patient at home. The necessary materials cost less than \$1.00.

One needs (1) a section of glass tubing to fit the fingers loosely (Fig. 2). We use a piece 5 inches long, of 1 inch internal diameter, $\frac{1}{16}$ inch wall, with flamed ends; (2) surgical drainage tubing 1 or $1\frac{1}{4}$ inches across when lying flat; (3) one No. 6 rubber stopper with hole bored to fit a (4) glass or metal connecting-tube running to (5) a rubber bulb with single opening and without valves ("blind bulb," $1\frac{1}{2}$ inches by $2\frac{5}{8}$ inches). This bulb should be chosen with some care as it must give negative pressure of 100 mm. Hg. All bulbs should be tested with a mercury manometer before buying or using them for this purpose.

The apparatus is assembled as shown in Figure 3. The drainage tube is employed as a cuff to make an air-tight joint between finger

and glass tube. Lanolin is used to make the joint between cuff and finger air tight. Tight constriction of the finger by the rubber is to be avoided and it is unnecessary. The bulb is attached when it is partly compressed. Suction is applied to the finger by allowing the bulb to expand, and pressure is applied by compressing the bulb with the fingers of the other hand.

Four patients with advanced thrombo-angiitis obliterans of the fingers have been treated, the patients taking the apparatus home with them, and giving the treatment themselves. Treatment consisted of suction for 10 seconds, then of pressure for a sufficient length of time to make the finger blanch. The patients were directed to use the apparatus for a half hour twice daily. In each instance, after 2 weeks to 3 months of treatment, a cold, blue, painful finger became warmer, its color improved, and pain disappeared. No proof of the value of this therapy can be claimed from so short a series of patients, but the principle of the method is similar to that of the accepted methods of Landis and Gibbon^{8a,b} and of Herrmann and Reid,⁵ for which considerable favorable evidence has accumulated.

No attempt has been made to apply this simple technique to the treatment of toes with occlusive arterial disease but there seems no doubt that it could be used in selected cases. The bulb could be connected by rubber pressure tubing which is long enough to permit the bulb to be held in the hand. If the circulation at the base of the toe is dangerously decreased by disease great care should be taken to avoid chafing from glass or rubber.

deTakats³ in a recent article implied close similarity between suction and pressure therapy and therapy by intermittent venous occlusion (Collens and Wilensky^{2a,b}), the criterion being similarity of color change. By means of the simple suction and pressure apparatus described above, one can illustrate very clearly the color changes in the fingers characteristic of suction and pressure. To study the effects of intermittent venous occlusion under comparable conditions a small inflatable cuff of thin rubber and silk was constructed for application to the base of the fingers. This cuff was rhythmically inflated with the pressures and timing advocated by Collens and Wilensky for the leg.

In normal fingers the suction phase of our apparatus produced reddening of the skin within a second while the pressure phase produced immediate blanching. In contrast to this intermittent venous occlusion caused a slow increase in skin color, and the skin became slightly cyanotic. Release of occlusion permitted slow return of normal color. In other words, the changes of color seen under suction and pressure are more rapid and intense than those produced by intermittent venous occlusion.

An Apparatus for Giving Drugs by Iontophoresis. Treatment by iontophoresis had a vogue about 40 years ago but it was soon largely

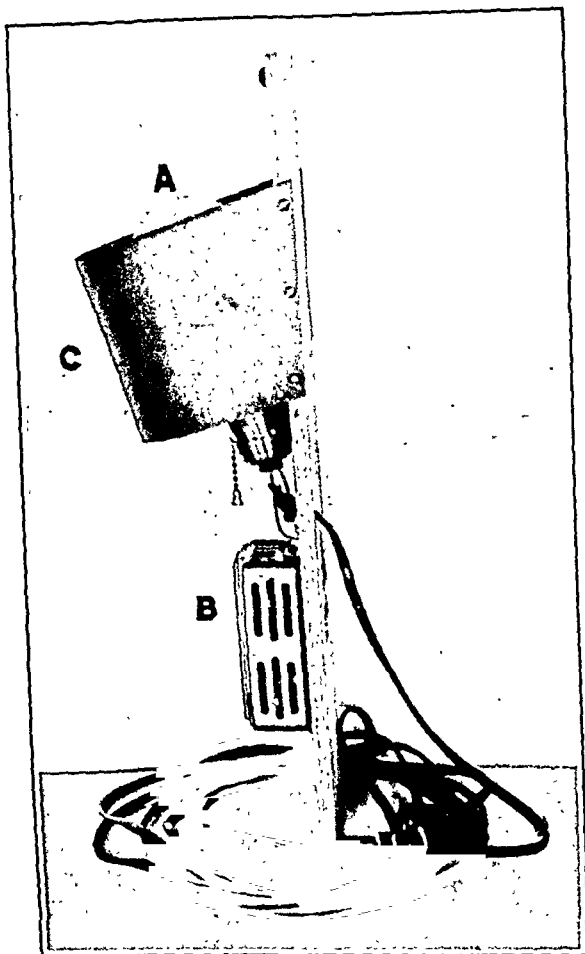


FIG. 1.—A simple thermoregulator for maintaining optimum temperature in a foot cradle. A, 60-watt bulb; B, thermostat; C, lamp guard.

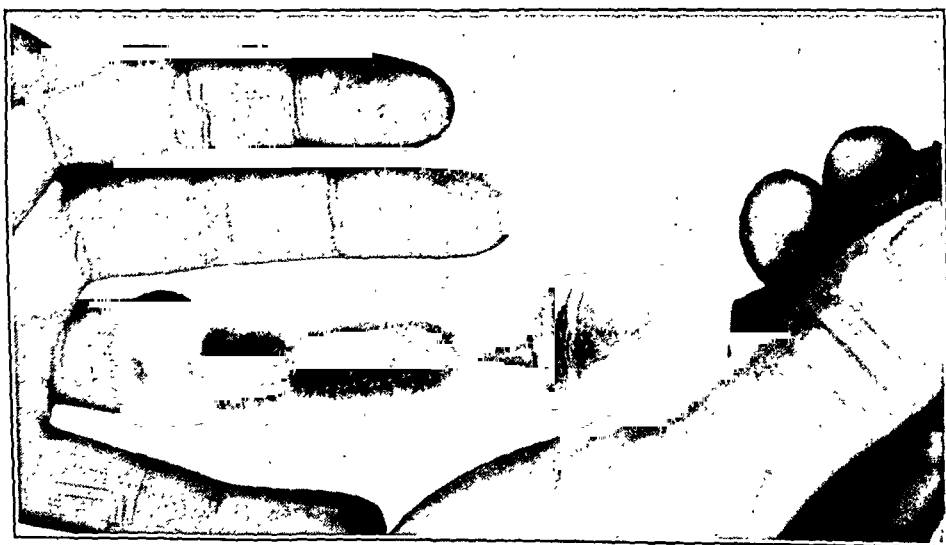


FIG. 2.—A simple apparatus for application of alternate suction and pressure to the fingers.

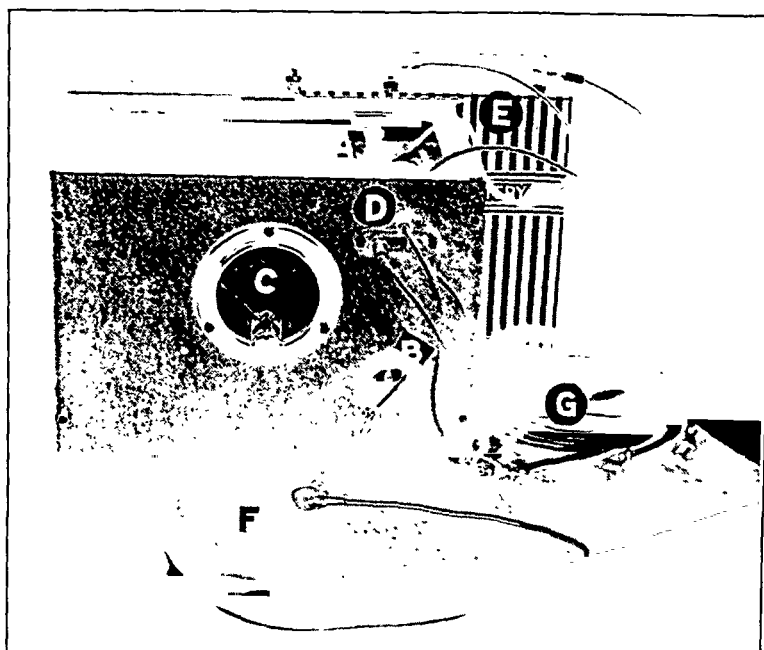


FIG. 3.—Apparatus for iontophoresis. *A*, portable battery; *B*, variable resistance; *C*, milliammeter; *D*, tip jacks; *E*, long-life battery; *F*, negative electrode; *G*, lead wires; *H*, alligator clips; *I*, terminal of negative electrode.

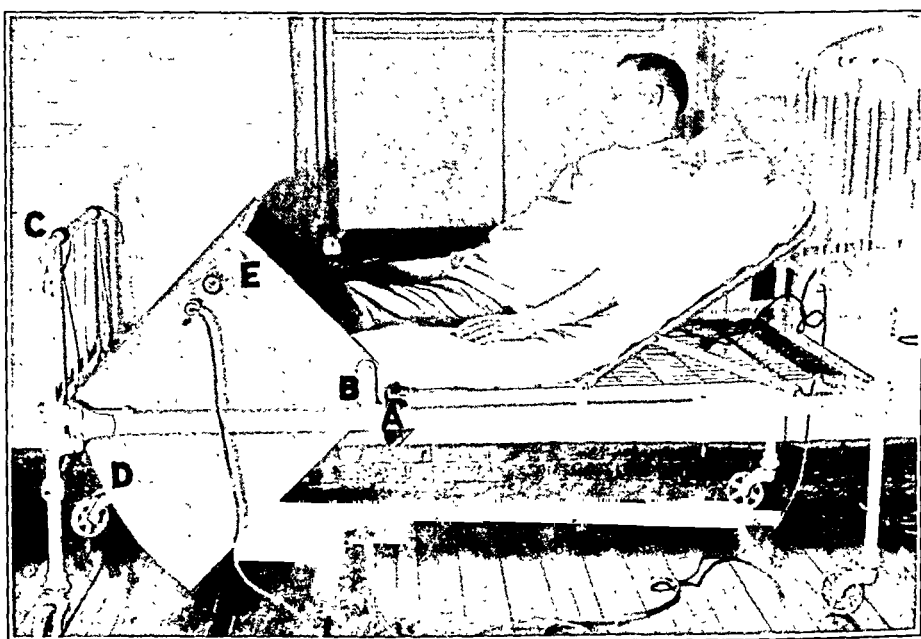


FIG. 4.—A bed altered to permit a dependent position of the legs (see text).

abandoned. Kovacs⁶ reopened the subject by introducing mecholyl iontophoresis for the treatment of arthritis. But the interest soon turned to its use in peripheral vascular disease.^{6,7,10,13} The necessary apparatus can be obtained from various manufacturers at a cost which has varied from \$125 to \$15. We have been using apparatus the parts of which can be bought at any radio supply store and assembled for about \$15.00. Ten of these outfits are now in use and have been entirely satisfactory.

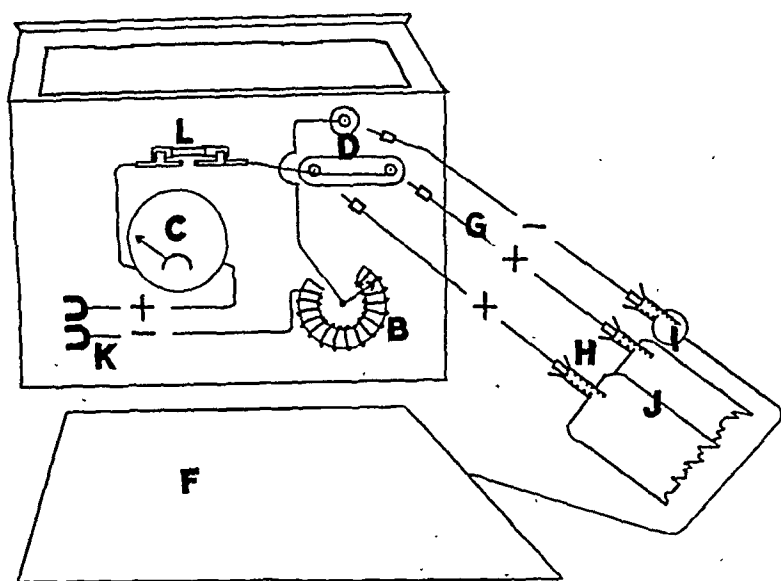


FIG. 3 A.—Apparatus for iontophoresis—Wiring Diagram. Designations by letter correspond to those in Fig. 3. J, metal sheeting of positive electrodes; K, spade lugs; L, fuse.

The parts are (1) a steel cabinet, 10 by 7 by 6 inches (Bud No. 993); (2) one 50 MA. milliammeter (Triplett No. 321); (3) one 10,000 ohm variable resistance (Yaxley E-10M-P) with knob; (4) one fuseholder and three $\frac{1}{16}$ ampere fuses (two are spares); (5) one 45V "B" battery (Burgess No. 5308) for use in the portable cabinet; or No. 21308, a larger battery, with a longer life, and so more satisfactory for use in the clinic. These batteries have three terminals labelled: "—", "+22.5", and "+45"; 22.5 volts can be drawn by using the terminal marked 22.5 and either of the other terminals. (6) One red single insulated tip jack (negative pole) and (7) one black twin insulated tip jack (positive pole); (8) 10 feet of red and 20 feet of black rubber-covered braided wire (Kinkless RC) for lead wires (to electrodes on patient); (9) one red and two black tip plugs for attaching one end of lead wires to tip jacks; (10) one red and two black insulated alligator clips for attaching the other end of the lead wires to the electrodes (2 positive, 1 negative), and (11) two

insulated spade lugs (one red, one black) for attaching two short wires (2 feet long) to the battery.

The apparatus is assembled as follows (Figs. 3 and 3A): The front panel of the cabinet is removed by taking out the screws shown at the four corners, and holes are cut to take the shaft of the variable resistance (B), the milliammeter (C), and the tip jacks (D). The fuse holder is fastened by a screw which shows 1 inch to the left of (D). A series circuit from the red (negative-upper) tip jack through the resistance, the battery, the ammeter, the fuse, and back to the black (positive-lower) tip jack is made by means of soldering lengths of insulated wire. The front panel of the cabinet is then replaced. A red wire with spade lug (K—Fig. 3, A) goes to the negative pole of the battery and a black wire and spade lug to the positive, marked 22.5 V. An 8-foot red (negative) and two 8-foot black (positive) lead wires (G) are used, with tip plugs on one end and alligator clips (H) on the other. Either the small, portable battery (A, Fig. 3), or the large long-life battery (E) may be used. A combined brace and compartment (not shown) is made by cutting a piece of wood to fit in the left end panel and attaching it vertically to another piece which wedges the small battery against the right end panel.*

A negative (indifferent) electrode (F., Fig. 3 or 3A), for application to the back of the thorax, is illustrated because we have seen none that seems as satisfactory. It consists of copper wire screening with edges heavily covered with sewed cotton tape, covered by oversize (to allow for shrinking) light duck. An end of rubber-insulated wire is braided and tied by cotton thread into one end of the copper screening. This electrode makes excellent contact, has long life, and we have seen no more than a mild erythema result when 10 to 35 milliamperes of current have been used. It cannot be bought, but can easily be made. Descriptions of satisfactory positive electrodes used to make contact between drug solution and the limb under treatment, can be found in papers by Kovacs,⁶ Kramer,⁷ and Cohn and Benson.¹ A common form consists of a 15 inch by 2½ inch piece of diathermy metal sheeting ("medium electrode foil" (obtainable from any Roentgen ray supply store), reinforced asbestos paper (Merck & Co.), and a 3 inch Ace Bandage.

Our experience in the use of iontophoresis is confined to the treatment with Mecholyl. The method to be described differs in no essential way from that used by others.^{6,7} The spade lugs are attached to the battery terminals. The lead wires (G) are attached by plugging into the tip jacks (D). All the resistance is thrown into the circuit by turning knob B counter-clockwise as far as it will go. A couch is covered with rubber sheeting and turkish towels.

* The Radio Department of the M. and H. Sporting Goods Store, 512 Market Street, Philadelphia, Pa., supplied these parts and assembled them for us at a total cost of \$15.40.

The negative electrode is prepared by soaking it and a hand towel in warm tap water. A small mat of rubber is laid on the turkish toweling which covers the couch, the electrode is placed on this and the wet hand towel is placed on the electrode. The patient, wearing only a hospital gown with an open back, reclines on the couch with the wet towel in contact with his back.

Either one or two positive electrodes can be used. The asbestos paper and the Ace bandage are soaked in a 0.2% solution of Mecholyl. The part to be treated is surrounded by one layer of wet asbestos paper. Two more layers, each a little larger than the metal sheeting, are laid on the first layer, and the metal sheet is laid on this triple thickness of paper. The bandage is firmly applied around all of the asbestos paper and all except one end of the metal sheet (J, Fig. 3-A), this end left free and the black lead wire clipped to it.

As an extra precaution against a short circuit, just before passing the current through the patient, the clip (H) of the red (negative) lead wire is made to touch momentarily the clip of a black (positive) lead wire, and the resulting deflection of the ammeter noted. If this is not more than 3 milliamperes the treatment is begun.

When the knob B turned counter-clockwise as far as possible, the clip of the red lead wire is attached to the terminal (I) on the negative electrode. In this way the circuit through the patient is completed. The current is increased slowly by turning the knob (B) clockwise, while the operator watches the needle of the milliammeter. Several minutes should be used in raising the current to the desired level. A strong prickling sensation at the positive or negative electrode indicates that tolerance has been reached, but this sensation becomes less and then more current can be tried. There should be no discomfort during treatment, and from 15 to 25 milliamperes can be used with safety in most cases. The chief danger lies in the burn which will result if the metal of the positive electrode slips off the underlying paper and gets into direct contact with the skin. The patients must be instructed to report any discomfort immediately.

Iontophoresis is usually given three times weekly for periods of one-half hour each time.

Mecholyl iontophoresis has been advocated in the treatment of varicose ulcers,¹³ chronic thrombophlebitis,¹⁰ scleroderma,⁴ and to some extent in the treatment of limbs with obliterative and spastic arterial disease.⁷ The first author's experience with treatment by mecholyl iontophoresis has been restricted to the treatment of 20 patients for periods ranging from 1 week to 1 year.* Of 8 patients with varicose ulcers 1 was unimproved, 3 were healed, and 4 much im-

* Thanks are expressed to Miss Sarah Turner for technical assistance in the treatments with mecholyl iontophoresis, and to Merck & Co., Rahway, N. J., for donating the mecholyl and the reinforced asbestos paper.

proved after treatment for periods varying from 1 week to 4 months. Of 8 patients with chronic thrombophlebitis, 7 were symptomatically relieved in from 1 week to 4 months. Of 4 patients with scleroderma 3 were definitely benefited in from 2 weeks to 8 months.

Only a few untoward effects were encountered. In an asthmatic patient with a varicose ulcer mecholyl iontophoresis (8 milliamperes of current) produced an asthmatic attack. In 1 patient with severe chronic thrombophlebitis and varicose veins, two treatments were followed by chills and fever. It is reasonable to suppose that bacteria or toxic materials were washed from diseased vessels into the general blood stream. It has been shown that the blood flow through a limb is greatly increased by mecholyl iontophoresis.⁹

A Bed Altered to Permit a Dependent Position of the Legs. Before the development of the device to be described some patients with peripheral vascular disease always insisted on hanging their diseased legs out the side of the bed, claiming that any other position was more painful. In several of these cases the reaction of the skin to histamine gave evidence that the circulation was better when the limb was dependent. This was in accord with theoretical expectations as the hydrostatic element in the blood pressure of the peripheral arteries must be increased when the limb is dependent. Pearse and Morton¹¹ have demonstrated this increased arterial pressure in the arteries of dependent legs of normal persons. The bed pictured in Figure 4 was designed to take advantage of this fact in the treatment of selected cases of peripheral vascular disease. It was constructed at the shop of the Johnson Foundation of the University of Pennsylvania under the direction of Mr. A. J. Rawson.

The spring of an old hospital bed was shortened to a point (A) 30 inches from the foot of the bed. A box fitting inside the spring frame was mounted on a hinged pedestal (B) so that it could be raised and lowered by cords (C) which were tied to the foot to support the free end at the desired height. The lower end of the mattress rested on the floor of the box.

The box was made by nailing a type of wall board, sold under the name of "Masonite," to a wooden frame. It contained two lights, shielded with Masonite guards, placed, one on each side, under the letter D. These were controlled by a DeKhotinsky Thermoregulator (Central Scientific Co.), the outer end of which is shown at the apex of the box (E). A switch is beside it. The total cost of the materials and labor necessary to alter the bed was about \$50.

When in use a blanket was placed over the box, so that one edge acted as a curtain to close the aperture through which the feet were inserted. The bed clothing was then thrown over the top of this blanket.

The bed has found its greatest usefulness in the treatment of patients whose pain is relieved by the dependent position. We allow such persons to choose the angle they find most comfortable. Most

of them have preferred to have their feet about 30 degrees below the horizontal when the back rest is down, 45 degrees or more when the back rest is elevated. The relief afforded is often quite striking.

Certain patients with peripheral vascular disease complicated by infected lesions, or by edema, have increased pain when the diseased leg is dependent. These patients are never treated with the legs in the dependent position. The legs may be held level, or elevated by raising the free end of the box.

Summary. Four types of apparatus used in the treatment of peripheral vascular disease at the Hospital of the University of Pennsylvania are described. Three of them are adaptations of devices previously described by other authors, and they are recommended only because they are simpler, more portable, and less expensive than the originals. We describe:

1. A simple thermoregulator, for use in foot cradles.
2. Simple inexpensive apparatus to permit the application of alternate suction and pressure to single digits.
3. Inexpensive apparatus for iontophoresis, constructed from standard radio parts.
4. A bed so altered that the legs can be within a thermoregulated cradle and at the same time be dependent, level or elevated.

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THE DIAGNOSIS OF TULAREMIA.

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DURING the past 2 years, a study of the cases of tularemia at this hospital indicated the need of rapid, yet reliable methods of diagnosis early in the course of the infection. This is particularly

true because the early administration of specific anti-tularenses serum is advocated for therapy.^{2d,i,j} An accurate diagnosis is necessary soon after the onset of the tularemic infection, if serum is to be given early.

A definite diagnosis of tularemia is dependent on laboratory procedures. The majority of the ulcero-glandular cases present a rather typical syndrome of contact history (rabbits, ticks), ulcer, marked adenitis, acute illness from 1 to 3 weeks and prolonged convalescence. Although the diagnosis usually can be suspected in these cases, confusion may arise with other infections producing a local ulcer with regional lymphangitis and adenitis. The other types of tularemia, particularly the typhoidal, glandular, and pulmonic forms, often do not present a characteristic clinical picture and are frequently mistaken for other disease entities which they may simulate. The most that the clinician can do in these cases is to suspect the possibility of a tularemic infection.

It is therefore apparent that laboratory procedures are necessary to confirm or establish the diagnosis of tularemia. A positive diagnosis of tularemia cannot be made without the use of one or more of the following diagnostic tests:

1. Blood agglutination.
2. Opsonocytophagic reaction.
3. Skin tests.
 - (a) Antigen skin test.
 - (b) Antiserum skin test.
4. Culture of organisms.

It is our purpose to present experience with these diagnostic tests in 50 cases of tularemia. We were particularly interested in the intracutaneous tests^{2b,c,g,h} as reported by Foshay, who considers these tests as reliable and diagnostic early in the course of the disease. We attempted to evaluate the various tularemia skin tests in correlation with the other diagnostic procedures commonly used in tularemia. The results of these tests are shown in Table 1. Some of the patients received all of the available tests, while in others it was possible to do only some of them.

Blood Agglutination. The test used in this work did not differ in essentials from that described by Francis and Evans.⁵ The antigen used was prepared by growing several strains of *Past. tularensis* (old stock cultures and a recently isolated strain) upon a nutrose-glucose-serum agar containing cystine.^{2c} The washed bacteria were killed by 0.4% formalin in 0.85% saline and suspended in saline to give a turbidity equivalent to 100 p.p.m. of kaolin in saline.

Apparently all cases of tularemia develop a positive agglutination—usually during the second week—which persists for the remainder of the life of the patient. All of our 50 cases had positive agglutinations. Those patients whom we saw soon enough for

early observations developed agglutinins during the second week and these gradually increased to a high titer. A titer of at least 1:80 is usually necessary for diagnosis, but lower values may be significant if there has been a previous negative agglutination or if there is a positive skin test and opsonocytophagic reaction. The agglutinin titer may be low several years after recovery from the initial infection (Cases 42 and 45). Cross-agglutination with *Br. abortus* and *B. proteus* OX₁₉ may cause some difficulty. Non-specific agglutination is usually present in a lower dilution and is slower in developing in the water bath. Differentiation is frequently possible by use of the opsonocytophagic reaction and the skin tests.

Opsonocytophagic Reaction. The phagocytic test was essentially the opsonocytophagic test described by Huddleson.⁸ The patient's blood (5 cc.) was added to 0.2 cc. of 20% sodium citrate. In some instances, when repeated tests were to be made on the same patient, 1 cc. of blood was added to 0.2 cc. of a 4% sodium citrate solution in saline, using a tuberculin syringe. The test was performed according to the procedure of Evans¹ and a phagocytic index number (P.I.N.) was obtained from the stained slide, using the nomogram of Foshay and LeBlanc.³ The antigen for this test was prepared by growing the organism on the nutrose-serum-cystine agar described by Foshay,^{2*} washing the growth with saline containing 0.4% formalin, and finally suspending in sufficient formalized (0.4%) saline to give a turbidity equivalent to 5000 p.p.m. of kaolin. Before use in the phagocytic test, a portion of this stock suspension was diluted ten times with sterile saline, centrifuged at 3000 R.P.M., and the supernatant fluid was replaced with an equal volume of sterile saline solution. In some instances, it was not possible to obtain the patient's citrated blood before the polymorphonuclear cells had disintegrated. In these cases, serum or plasma from these patients was mixed with equal volumes of the *Past. tularensis* suspension (500 p.p.m. kaolin), and citrated blood from a normal individual (rabbit blood served in some instances). Comparative tests, using this modification and the test as used by Foshay, showed no significant difference between the phagocytic index numbers obtained. The use of serum or plasma* (mixed with fresh citrated blood from a normal individual) for phagocytic tests may prove to be of value to health department laboratories receiving many specimens by mail too late for performance of the opsonocytophagic test as described by Huddleson.⁸

This test becomes positive about the same time as the blood agglutination. The reaction is usually strong after the third or fourth week of the disease and apparently persists as long as the agglutination (Cases 42 and 45). Interpretation of the phagocytic reaction has been quite difficult in some cases. We have observed many weak or even an occasionally strong phagocytosis in a number

* This method is to be published.

of conditions other than tularemia, so that a positive opsonocytophagic reaction in itself is not diagnostic.

The phagocytic reaction serves as an aid to the blood agglutination and skin test, particularly in those cases which have a questionable clinical diagnosis. The test is of value when there is a cross-agglutination between *Past. tularensis* and the Brucella group. Foshay^{2a} states that he has never observed an instance of cross-phagocytosis in patients who cross-agglutinated with either Brucella organisms or *Past. tularensis*. He considers this a most useful test for verifying the coexistence of these two diseases or for excluding one from the other.

The phagocytic reaction was usually strong after 2 or 3 weeks in the course of the illness, regardless of the clinical condition of the patient. However, in a few cases the reaction was weak in patients who were not reacting favorably to the infection.

Skin Tests. There are two main types of tularemic skin tests as described by Foshay—the antigen^{2c,d} and antiserum.^{2b,h} According to Foshay, these skin tests are diagnostic for tularemia from the first day of illness to at least the twenty-second year after complete recovery, or apparently the remainder of the life of the patient.

Antigen Skin Test. An intracutaneous injection of a suspension of detoxified *Past. tularensis* organisms (treated by formalin and nitrous acid^{2f} according to Foshay) was used for this test. The suspension was equivalent to 50 p.p.m. of kaolin and 0.05 cc. was injected intracutaneously. This antigen was used also for treatment of chronic cases and for immunization of animals for the production of diagnostic and therapeutic antisera. In our work, a suspension of Brucella organisms was used simultaneously as a control skin test.

A positive test is a delayed tuberculin-type of reaction, consisting of erythema and induration. It is read in 48 hours. The reaction is usually quite marked with local tenderness, without constitutional reaction, and tends to persist for from a few days to several weeks. This type of skin test appears to be specific and diagnostic early in the disease. The test was used in 32 proven cases of tularemia and was positive in all. In our experience, the test was positive in the first week of the disease (Cases 3, 12, 21, 23, 26, 30 and 36) and reacted positively several years after the onset of the infection (Cases 41, 44 and 48). A few normal individuals developed a slight nonspecific reaction which resembled the weakly positive reaction observed in some tularemic patients early in the infection. A nonspecific reaction usually faded rapidly after 36 to 48 hours, while a specific reaction generally persisted for a week or longer. A doubtful reaction should be repeated with the same antigen or a more concentrated suspension. It is important that the individual who observes the skin test reaction in the patient be familiar with the doubtful or non-specific reactions which a given antigen may produce in normal individuals. The usual case of tularemia will show

an unquestionable reaction with marked induration and erythema. In colored patients, this test was of definite value (Cases 46 and 47), whereas the antiserum skin test could not be read in deeply pigmented skins. The antigen skin test was positive even when the horse and goat antiserum skin tests were negative (Cases 35, 36 and 37). We have not seen a negative antigen skin test in a patient with a proven tularemic infection. We have checked this skin test in a large number of normal patients and in numerous clinical conditions and have found it to be one of our most reliable tests.

Antiserum Skin Test. The intracutaneous injection of specific tularensen antiserum was described by Foshay^{2b,h} as a diagnostic test for tularemia, suitable for use early in the course of the disease. The response in patients with tularemia to an intracutaneous injection of a 1 to 10 dilution of the antiserum is the production of erythema and edema at the site of injection, the maximum reaction occurring in 20 to 30 minutes. A control intracutaneous injection of a 1 to 10 dilution of normal serum should show no erythema or edema. It is essential in this test that a suitable control serum be used, but as emphasized by Foshay^{2h} it is necessary to use great care in the selection of animals for normal serum as well as for the production of reliable diagnostic antiserum if one wishes to avoid non-specific reactions in the diagnostic test. We have used commercial (Mulford-therapeutic) antitularensen horse serum,* antitularensen goat serum (received from Foshay), and human convalescent serum obtained from some of our tularemia patients.

In our experience, if the antiserum test showed a definite positive reaction and the control serum was negative, a diagnosis of tularemia could be made and was always substantiated later by the blood agglutination and the antigen skin test. If the control serum showed even a mild reaction the test was of no value, regardless of how intense the specific antiserum reaction might be. Of the positive control reactions, many did not show a typical allergic response, with urticarial wheals, itching, and so on, and the conjunctival test for sensitivity to the control serum was usually negative. The response to an intracutaneous injection of this control serum was an erythematous-edematous reaction.

The antitularensen horse serum (Mulford-therapeutic) skin test was employed in 35 cases of proven tularemia (Table 1). This test was diagnostic in 12 cases, but in 20 the patients exhibited positive control reactions. Three cases showed no reaction to either serum or to the control test. The test was therefore of value in only about one-third of our patients. The test was diagnostic early in the disease before the blood agglutination was positive (Cases 1, 3, 4, 6, 9 and 12) and later (Cases 2, 5, 10 and 11). Antitularensen goat serum (received from Foshay) was used on 21 proven cases of tularemia.

* This product was supplied to us through the kindness of Dr. W. A. Feirer of Sharp & Dohme (Mulford Biological Laboratories).

TABLE 1.—RESULTS OF DIAGNOSTIC TESTS IN TULAREMIA PATIENTS.*

Case No.	Day of disease.	Blood agglutination titer.	Opsonocytophagic reaction.	Skin tests.				Antigen.
				Horse tularenses anti-serum.	Horse control serum.	Goat tularenses anti-serum.	Goat control serum.	
1 . . .	3	Neg.	++++	Neg.			
	7	1:20						
	24	1:320						
2 . . .	55	1:320	++++	Neg.			
3 . . .	6	Neg.	++++	Neg.	++	+++	++++
	13	1:160						
	43	1:640	Strong					
4 . . .	12	Neg.	+++	Neg.			
	20	1:320						
	45	1:5120						
5 . . .	21	1:1280	+++	Neg.			
6 . . .	8	Neg.	+++	Neg.			
	11	1:320						
7 . . .	7	1:640	+++	Neg.			
8 . . .	11	1:320	+++	Neg.			
9 . . .	5	Neg.	+++	Neg.			
	17	1:320						
10 . . .	20	1:640						
	56	1:320	++	Neg.			
11 . . .	20	1:320	++	Neg.			
12 . . .	6	Neg.	Neg.	+	Neg.	+	Neg.	++++
	69	1:800	Strong					
13 . . .	7	Neg.	++++	+			
	12	1:320						
14 . . .	5	Neg.	+++	+	++	Neg.	
	10	1:320						
15 . . .	15	1:640	+++	+			
	28	1:640						
16 . . .	42	1:5120	Strong	+++	+	+	++	+++
17 . . .	52	1:320	+++	+			
18 . . .	15	1:640	Strong	++	+	++	++	++++
	34	1:640	Strong					
19 . . .	40	1:1280	Strong	++	+	++	++	++++
	80	1:640	Strong					
20 . . .	17	1:80	Moderate	++	++	++	++	++++
	44	1:1280	Strong					
	137	1:5120	Strong					
21 . . .	7	1:160	Strong	++	++	++	++	++++
	35	1:400	Strong					
22 . . .	8	1:160	++++	++			
23 . . .	7	1:40	+++	++	+++	Neg.	++++
	30	1:640						
24 . . .	5	Neg.	++++	+++			
	18	1:320						
25 . . .	17	1:2560	Weak	+++	+++	+	+	++++
	81	1:800	Strong					
26 . . .	7	1:40	Weak	+++	+++	++++	Neg.	++++
	67	1:640	Strong					
27 . . .	1	Neg.	Neg.					
	10	1:80	Neg.	+++	+++	+++	Neg.	+
	90	1:800	Strong					
28 . . .	12	1:40	+++	+++			
	14	1:80						
29 . . .	23	1:5120	Strong	++++	++++	++	Neg.	++++
30 . . .	7	1:640	++++	++++	++++	Neg.	++++
	30	1:3200	Strong					
31 . . .	25	1:1280	++	+++			
32 . . .	21	1:640	Strong	++	++++	+++	Neg.	++++
	26	1:3200						
33 . . .	16	1:6400	Strong	++++	++++	++++
34 . . .	16	1:3200	Weak	++++	++++	++++
35 . . .	10	1:40	Neg.	Neg.	Neg.	Neg.	++++
	20	1:80	Moderate	Neg.	Neg.	Neg.	Neg.	
	52	1:1600	Strong					
36 . . .	4	Neg.	Neg.	Neg.	Neg.	Neg.	++++
	13	1:320	Weak	Neg.	Neg.	Neg.	Neg.	
37 . . .	130	1:2560	Neg.	Neg.	Neg.	Neg.	++++
38 . . .	21	1:2560	Strong	++++
39 . . .	1½ yrs.	1:80	Strong	++++
40 . . .	1½ yrs.	1:160	Strong	++++
41 . . .	4 yrs.	1:80	Weak	++++
42 . . .	1½ yrs.	1:320	Strong	+	++	+
43 . . .	330	1:800	Strong	++++
44 . . .	6 yrs.	1:40	Moderate	++++
45 . . .	6 mos.	1:640	V. strong	++++
46† . . .	40	1:320	±	±	±	±	++++
47† . . .	90	1:2560	Strong	±	±	±	±	++++
48 . . .	4 yrs.	1:320	Strong	++++
49 . . .	35	1:1280	Strong	++++
50 . . .	30	1:640	Strong	++++

* The degree of reaction is graded from + to +++++; the + indicating a mildly positive reaction, the +++++ a markedly positive reaction.

† 1:10 dilution of antigen used in this case.

‡ Colored patients.

It was diagnostic in 8 cases while 10 showed a positive control reaction and 3 gave no reaction to either antiserum or normal control serum. The use of convalescent human serum as a skin test has been entirely unsatisfactory in our hands. Serum was obtained from 3 patients who had completely recovered from a recent tularemic infection. The reactions obtained in normal and tularemic patients were variable and unreliable.

The diagnostic antiserum skin test deserves further study. The value of the test has been demonstrated here frequently, but its usefulness has been limited in our work because we have been unable to find suitable control sera. Among the few animals available for experimental work, we have been unable to find any whose sera did not give edematous-erythematous reactions in many normal individuals. In our experience, the test has been of aid in about one-third of the patients because of non-specific reactions.

Culture of Organisms. Although the culture of *Past. tularensis* from an infected patient affords the most definite diagnosis of tularemia, the method usually requires animal inoculation with consequent hazard to non-immune laboratory workers. The disease is easily transmitted from an infected animal to man, regardless of the precautions taken. Francis⁴ states that 41 workers in 13 laboratories in the United States, England, Japan and Russia contracted the disease performing necropsies on infected guinea-pigs and rabbits or from handling infected living ticks. The culture of *Past. tularensis* requires so much time that it is of little value to the clinician interested in specific serum therapy early in the course of the disease. The other methods of diagnosis are so reliable that culture of the organism is rarely necessary.

Previous Infection. The possibility of a previous tularemic infection must be eliminated, since the blood agglutination, opsonocytophagic reaction and the skin tests remain positive for years after recovery from the initial infection. The clinical history, physical findings of an active tularemic infection, a rapidly rising blood agglutinin titer, and culture of *Past. tularensis* from the lesions are the most important means of differentiating a previous tularemic infection from one recently acquired.

Effect of Tularense Antiserum on Diagnostic Tests. A diagnosis of tularemia was made on a number of patients during the first week of the illness on the basis of skin tests, before the blood agglutination was positive. These patients received therapeutic anti-tularense serum and during the second week of the illness developed positive agglutinations of a high titer. The question arose as to whether or not the serum itself could cause a positive blood agglutination in a non-tularemic patient and that perhaps some of these cases treated on the basis of a positive skin test did not have tularemia.

Three normal individuals were tested for agglutination and phago-

cytosis of *Past. tularensis*. On the following day each received 15 cc. of commercial therapeutic antitularens horse serum, intravenously. Five minutes and 1 hour, as well as 24 hours later, blood specimens, were obtained and tested for agglutination and phagocytic activity. The following day (immediately following removal of the 24-hour blood specimen) an additional 15 cc. of antitularens horse serum was given intravenously. Blood specimens taken 5 minutes, 1 hour and 24 hours later, were tested for phagocytosis and agglutination of *Past. tularensis*. The commercial antiserum employed had an agglutination titer of 1 to 320 against the antigen used in the agglutination tests and induced a very strong phagocytosis of *Past. tularensis* organisms when added to citrated blood from a normal individual. The results of the test are shown in Table 2. Case 1

TABLE 2.—EFFECT OF ANTITULARENSE SERUM (HORSE) ON AGGLUTININ TITER AND OPSONOCYTOPHAGIC REACTION IN NON-TULAREMIC PATIENTS.

			1st injection 15 cc. antiserum intravenously.			2d injection 15 cc. antiserum i.v. (24 hrs. after 1st injection).				
	Case No.	Before antiserum.	5 min. after.	60 min. after.	24 hrs. after.	5 min. after.	60 min. after.	24 hrs. after.	7 days after.	14 days after.
Agglutinin Titer.	1	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
	2	Neg.	1:20	1:20	1:20	1:20	1:20	1:20	1:10	1:20±
	3	Neg.	Neg.	Neg.	1:5	1:5±	1:5	1:5±	Neg.	Neg.
Opsono-cytophagic reaction.	1	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
	2	Neg. (P.I.N. 5)	Moderate (P.I.N. 48)	Neg. (P.I.N. 2)	V. Strong (P.I.N. 88)	V. Strong (P.I.N. 86)	V. Strong (P.I.N. 90)	V. Strong (P.I.N. 86)	Neg. (P.I.N. 14)	Neg. (P.I.N. 4)
	3	Neg.	Moderate (P.I.N. 46)	Moderate (P.I.N. 58)	Neg. (P.I.N. 10)	Neg. (P.I.N. 10)	Neg. (P.I.N. 4)	Weak (P.I.N. 20)	Neg.	Neg.

Note: *Brucella abortus* agglutination and phagocytosis tests were all negative.

showed no agglutination or opsonocytaphagic reaction following this serum. Cases 2 and 3 developed very weak agglutination titers which were practically negative after 2 weeks. The opsonocytaphagic reaction showed an interesting transitory reaction, particularly in Case 2, but was negative in all 3 cases after 14 days. Although only 3 subjects were used in this experiment, it seems that antitularens serum therapeutically has little or no effect in producing a positive blood agglutination, but may cause a transitory opsonocytaphagic reaction.

Effect of Antigen Skin Test on Diagnostic Tests. Goldstein,⁶ Heathman,⁷ and Evans¹ have shown that intracutaneous tests with heat-killed *Brucella* suspensions or purified nucleoprotein stimulate the production of agglutinins in a large percentage of subjects. Since the *Past. tularensis* antigen skin test is used early in the course of the disease, before the blood agglutination is positive, it is important to know whether the intracutaneous test itself can stimulate

the production of opsonins and agglutinins. The sera of 12 patients (tuberculous) were tested for phagocytic activity as well as agglutination of a *Past. tularensis* antigen before being given an intracutaneous injection of 0.05 cc. suspension of detoxified *Past. tularensis* organisms (50 p.p.m. kaolin turbidity). Two weeks later specimens of blood were drawn for phagocytic tests and agglutination reactions. A second intracutaneous injection of the detoxified antigen was given at this time. The results of these tests are shown in Table 3. Four of the 12 patients developed positive agglutinations, the highest of which was 1 to 40. An initial agglutination of 1 to 20 in 1 patient was increased to 1 to 40 following the intracutaneous test. Two patients developed weak opsonocytophagic reactions. These

TABLE 3.—EFFECT OF ANTIGEN SKIN TEST ON BLOOD AGGLUTINATION, PHAGOCYTOSIS, AND SUBSEQUENT SKIN TESTS IN NON-TULAREMIC PATIENTS.

Case No.	Before vaccine skin test.			14 days after skin test.			
	Blood agglutination titer.	Opsonocytophagic reaction.	Reaction to initial skin test.	Blood agglutination titer.	Opsonocytophagic reaction.	Reaction to second skin test.	
1	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
2	Neg.	Neg.	Neg.	1:20 ±	Neg.	Neg.	Neg.
3	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
4	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
5	Neg.	Neg.	Neg.	1:40+ +	Weak	±	
(P.I.N. 32)							
6	Neg.	Neg.	Neg.	1:20 ±	Weak	±	
(P.I.N. 25)							
7	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
8	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
9	1:20+ +	Neg.	Neg.	1:40+ +	Neg.	Neg.	Neg.
10	Neg.	Neg.	Neg.	1:20 ±	Neg.	Neg.	Neg.
11	Neg.	Neg.	±	Neg.	Neg.	Neg.	Neg.
12	Neg.	Neg.	±	Neg.	Neg.	Neg.	Neg.

NOTE.—Agglutination reactions and phagocytosis tests of patients' serum for *Br. abortus* were negative throughout.

2 patients also developed mildly positive skin tests. It is apparent then that the effect of the tularensis antigen skin test on the blood agglutination and phagocytic reaction is almost negligible.

Conclusions. 1. The results of diagnostic tests in 50 cases of tularemia are presented.

2. The blood agglutination is the most constant and reliable diagnostic method after the first week of the disease.

3. The antigen skin test is positive during the first week of the disease and appears to be highly specific and reliable.

4. The antiserum skin tests, both goat and horse, have been of value in only a small percentage of cases, because of non-specific reactions of control sera. It is always necessary to use a control serum in this test.

5. The opsonocytophagic reaction tends to parallel the blood agglutination in time of appearance and is valuable in differentiating Brucellosis from tularemia, when cross-agglutination occurs.

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SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS.

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IN 1937 Louis Hamman⁴ described for the first time a group of cases with a syndrome resulting from the *spontaneous* development of interstitial emphysema of the lungs, and it is appropriate that this interesting clinical entity should be designated as "Hamman's Disease."

Mediastinal emphysema resulting from trauma or pulmonary disease was recognized more than a hundred years ago. Laennec⁵ described curious grating sounds and bubbling râles during respiration as diagnostic signs of subpleural and interlobar emphysema of the lungs. These signs were later confirmed by Skoda,⁹ while Rokitansky⁸ described the pathologic anatomy of mediastinal emphysema following ulceration of the trachea, and pulmonary trauma. Other observers reported that the condition was occasionally *secondary* to pertussis, croup, severe crying, the labor of child bearing, bronchial asthma, straining at stool, the induction of artificial pneumothorax, and pneumonia, especially the post-influenzal pneumonia of the 1918 epidemic. Müller⁷ in 1888 described certain clinical aspects of mediastinal emphysema, noting the presence of fine bubbling crepitations synchronous with the heart's action, and observing the disappearance of cardiac dullness. Müller pointed out that the diagnosis was greatly facilitated by the appearance of subcutaneous emphysema.

During the World War the term "pericardial knock" was introduced by Smith,¹⁰ who suggested that a curious sound occasionally heard over the precordium in cases of penetrating wounds of the chest was caused by "air in the interstitial connective tissue of the lung."

In 1928 Lister⁶ reported a single case which in all likelihood was an instance of spontaneous interstitial emphysema of the lung, but believed that the "pericardial knock" originated from "partial obstruction of the pulmonary artery by tension or distortion caused by displacement of the lung."

Wolferth and Wood¹¹ observed an instance of "pericardial knock" associated with spontaneous pneumothorax, but the sounds were no longer audible when they examined the patient several days after the onset of the pain. The sounds were said to have been heard by observers across the room 2 days after the pain appeared.

Achard¹ has produced mediastinal emphysema in dogs experimentally by: 1. Injection of air into the mediastinum; 2. Injection of air directly into the lung or the pleural cavity; 3. Subcutaneous injection of air; 4. Partial tracheal obstruction with a tracheotomy tube in place.

An excellent description of the surgical aspects of mediastinal emphysema is presented by Graham, Singer, and Ballon.³

Interstitial emphysema of the lungs is caused by the rupture of alveoli or bronchioles and the escape of air into the interstitial tissue of the lungs. If a large amount of air escapes it may travel along the interstitial bands toward the hilum and enter the mediastinum. A second and perhaps commoner pathway for the air to follow is to pass outward directly to the pleura along interstitial bands where it causes the formation of a bleb which may rupture and produce an ordinary pneumothorax. The air may go in both directions, producing both results.

The spontaneous type of interstitial emphysema described by Hamman is characterized by the sudden development of severe pain in the chest without antecedent trauma or unusual effort. The presence of a "peculiar crunching, crackling, bubbling sound heard over the heart with each contraction" is pathognomonic; additional evidence is afforded by the disappearance or decrease in width of the area of cardiac dullness. The presence of subcutaneous crepitation makes the diagnosis obvious and in certain cases pneumothorax is present. Air may be demonstrated in the mediastinum by Roentgen ray.

Since we have been able to find only 1 certain and 1 probable case report besides the 6 cases described by Hamman, and as interstitial emphysema must be exceedingly common and frequently overlooked, we have thought it of interest to describe in some detail one case which we feel was "spontaneous" and an additional case of interstitial emphysema following labor in a patient with rheumatic heart disease, as the physical findings and clinical picture seem to be identical, whether the condition originates "spontaneously," or from sudden increase in intrapulmonary pressure associated with vigorous or violent exercise.

Case Reports. CASE 1.—At 4 o'clock in the afternoon, a 17-year-old girl, apparently in perfect health, while dribbling a basket ball on the floor of her school gymnasium, was seized with a severe pain in the left chest. Because of the pain she returned to her home and went to bed. Shortly afterwards she heard a curious noise in her chest and told her mother that she thought she had pleurisy. When seen at 8 o'clock the patient was quietly reading a book and did not appear to be acutely ill. She stated that the pain increased when she lay on the left side, and that the noises in her chest "come and go." The pulse was 80, respirations were 18, temperature 98.4°, blood pressure 130/80. The only finding of interest on physical examination was the presence of distant soft crepitant sounds, localized to the precordium and of maximal intensity beneath the middle third of the sternum. There was definite association of these sounds with the cardiac contractions, but they occurred both in systole and diastole. Remembering Hamman's description of interstitial emphysema, the possibility of this diagnosis presented itself. At this time, however, it seemed more likely that the sounds were caused by acute fibrinous pericarditis, even though the "rub" was not quite characteristic. On the following day when the patient was seen the diagnosis was clear, for the characteristic bubbling, crunching, crepitant sounds, described by Hamman, were so distinctive as to admit of no other interpretation. The pain in the chest was much less intense. However, with changes of position the patient could modify the intensity of the curious sounds and also influence the severity of the pain. At certain times the sounds within the chest were heard at a distance of several feet by the patient's mother.

The white blood cells numbered 11,000. The electrocardiogram was normal. By evening the temperature was 99°.

The following morning the bubbling, crunching noises were slightly louder, but the patient seemed more comfortable. The area of absolute cardiac dullness was now completely absent and both sides of the chest were hyperresonant to percussion. The breath sounds were normal except at the extreme left apex, where they were somewhat distant.

On the next morning (the third day following the onset of the pain in the chest) the patient was brought by ambulance to the Holmes Hospital.

On admission the physical findings were described by Doctor F. Post, the resident physician, as follows:

"There is a definite limitation of expansion of the left side. On deep inspiration there were audible and palpable crackles which sound like a piece of newspaper being wrinkled. These sounds are maximum to the left of the sternum at the level of the third rib. Percussion note slightly more booming on the left than on the right. Impossible to obtain cardiac borders of dullness due to the booming percussion note. Heart sounds quite distant. No thrills, murmurs or frictions."

For the first time, slight but definite crepitation was felt in the skin overlying the sternum. This disappeared in 3 hours, and did not recur.

Roentgen ray of the chest was (Dr. H. G. Reinecke) as follows:

"Chest examination reveals a small pneumothorax on the left side with the top of this lung being retracted downward through a distance of 3 to 4 cm. Along the lateral chest wall the collapse is seen to almost the mid-thorax. No fluid is shown. On the right no pneumothorax is seen. On the lateral view air is seen in the soft parts of the anterior thoracic wall and possibly also in the anterior mediastinum. No air is seen over the shoulder areas or in the soft parts of the neck."

On the third hospital day the crackling sounds had completely disappeared, but on the following day there was a reappearance of the crackles associated with slight pain. At this time it was noted that the pulmonary second sound was greatly exaggerated on both palpation and auscultation.

The following day all abnormal physical findings except for the hyper-resonant percussion note had disappeared and the Roentgen ray showed complete disappearance of the pneumothorax and of the air in the mediastinum. The temperature was 99° on the evening of the second day in the hospital; from this time the temperature remained normal. On the tenth hospital day, the patient was discharged from the hospital. After a week of rest at home without symptoms she returned to school and has been entirely well to date. A Roentgen ray of the chest May 5, 1938, showed no abnormalities.

CASE 2.—M. B. (No. 81106), a 39-year-old white American housewife, was transferred to the Medical Service of this hospital from the Obstetrical ward on November 8, 1937, because of the sudden onset of a sharp pleuritic pain in the left chest which began 15 minutes following a difficult labor at which twins were delivered. The patient's past history revealed that she had "growing pains" in the legs at the age of 9, and 18 months before admission had had some vague arthritic pains in the right hip. There had been no fever or tachycardia and she had not been in bed. During the last half of her pregnancy detection of the characteristic murmurs led to a diagnosis of mitral stenosis. There were never any signs of cardiac failure. At this time she had come to the prenatal clinic because of a sore, red tongue. A microcytic anemia with hemoglobin of 8.5 grams and red count of 3.3 million was detected. On a high caloric, high vitamin diet with supplements of brewers' yeast and iron, the tongue returned to its normal condition and the anemia responded well. One month before delivery, twin pregnancy was diagnosed by palpation and confirmed by Roentgen ray.

The obstetrical note reveals that "the membranes were ruptured 5 hours before delivery. The first stage of labor lasted 8 hours; the second, 2 hours; the last, 6 minutes." The labor was extremely difficult for a para VI. Fifteen minutes after delivery, when the patient had returned to the ward, she experienced a sudden, sharp, stabbing pain in the precordial region which radiated directly through the chest to the back, where it was most intense at the region of the inferior angle of the left scapula. The pain was made worse by deep breathing or moving to either side or sitting up. It was relieved but not abolished by a fourth of a grain of morphine. She was seen 4 hours later by the medical consultant, who made a diagnosis of rheumatic heart disease with mitral stenosis and insufficiency, well compensated. The adventitious sounds heard in the precordial region were interpreted as the friction rub of an acute pericarditis and pleuropericarditis, probably on the basis of an acute rheumatic pancarditis. She was then transferred to the medical service.

The physical examination revealed a well developed and adequately nourished white female of 39 years, lying quietly flat in bed and in no pain so long as she remained quite still. Mouth temperature was 99° F., pulse 90, respirations 20, and blood pressure 114/78. The color was good and there was no evidence of shock. Except for enlarged tonsils and lactating breasts the findings of interest were limited to the chest and heart. Inspection revealed respirations which were regular and easy, but shallow. There was a decrease in expansion of the left chest with more pronounced splinting on deep breathing. Both sides of the diaphragm moved equally but the excursion was only moderate. Tactile fremitus was equal on both sides and there was no subcutaneous crepitation anywhere. Percussion elicited no abnormality. There was no evidence of pneumothorax or mediastinal shift. Breath sounds were vesicular and no râles were heard. The apex beat of the heart could be seen and felt in the 5th interspace in the mid-clavicular line, 7 cm. from the midline, just inside the left border of percussion dullness, which measured 8 cm. on the left and 3 cm. on the right. At times a vibration could be felt in the 3rd left interspace near the sternum.

It was easily obliterated by pressure in the area and this was associated with an alteration in the adventitious sounds. The heart sounds were regular and of good quality. At the apex, the second sound was split and there was a high pitched systolic murmur transmitted to the axilla. There was a low rumbling late diastolic murmur. The second sound at the base was accentuated on both sides, slightly louder in the aortic area. An unusual adventitious pleuropericardial sound, clicking, crunching, grating, but not bubbling, could be heard over most of the precordium, loudest over the second and third interspaces on the left. Though louder in systole, it was audible in diastole. It was heard best when the breath was held in deep inspiration (and this was painful), but was present in every phase of the cardiac or respiratory cycle. The intensity of this sound varied from time to time, being quite loud an hour after the onset of the pain and gradually decreasing for 48 hours. At this time the patient was moved about considerably in the process of taking Roentgen rays. This was associated with a great increase in the intensity of the sounds, and the pain which had markedly diminished came back with increased severity. Following this, the sounds gradually decreased so that they were barely audible on the 5th day after onset, but not thereafter. The Roentgen rays taken on the 3rd and 7th days of the illness did not show any pneumothorax or interstitial emphysema in the antero-posterior, lateral or either oblique views. The leukocyte count varied from 6900 to 10,500 per c.mm. with a normal differential. The urine was negative save for a few epithelial cells and leukocytes. Mouth temperature varied between 98 and 99.8° F., the pulse from 80 to 100, and respirations from 20 to 25.

The patient, seen 3 months following the episode, was quite healthy and normal in every way and had suffered no recurrence of the pain.

Discussion. The mechanism responsible for the auscultatory findings of interstitial emphysema is probably dual. When the air which has escaped along the interstitial connective tissue bands collects beneath the visceral pleura in the region of the heart, blebs are formed and the crunching sounds heard in patients with this disorder have been duplicated by us experimentally in dogs. However, it is highly probable in clinical cases that air having reached the anterior mediastinum finds its way between the spaces of the areolar tissue and when impinged upon by cardiac contractions causes crepitation.

These cases illustrate very clearly the essential clinical picture of this syndrome. In the second case, the onset came shortly after the severe strain of labor. In the other case, symptoms occurred while the patient was engaged in a very mild form of exercise involving no strain whatsoever. In neither case was there any clinical evidence of serious constitutional disturbance commensurate with the auscultatory signs, no shock, no cyanosis, no sweating and no tachycardia. Both cases, interestingly enough, were females, while all of Hamman's were males. In both cases the diagnosis was made by detection of the crunching, crackling, bubbling sounds and pain over the heart. We believe that it should be stressed that these sounds show great spontaneous variation in quality and intensity during the progress of the illness and may not be characteristic at all times. They also vary with change in position of the patient. In these

TABLE 1.—CLINICAL DATA IN RECORDED CASES OF SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS.

	Hamman, Case 1.	Hamman, Case 2.	Hamman, Case 3.	Hamman, Case 4.	Hamman, Case 5.	Hamman, Case 6.	Lister, Case 7.	Wolferth and Wood, Case 8.	This series, Case 1.	This series, Case 2.
Age	51	17	25	35	29	16	31	21	17	39
Sex	M	M	M	M	M	M	M	M	F	F
Color	W	W	W	W	W	W	W	W	W	W
Temperature	N	101.2	99.4	99.0	99.8
Pulse	N	116	96	96
Respirations	N	145/90	20	20
Blood pressure	N	130/80	114/78
White blood cells	N	13,000	N	N	28,500 to 5000	11,000	6900 to 10,500
Pain	Severe in chest	Severe in neck and chest. Painful swelling.	Sharp in left side of chest	Very severe in left chest	Very severe in left chest	Severe in right lower chest	Severe in upper chest	Pain in chest on exertion	Moderate in left anterior chest	Very severe in lower left chest
Duration	Bad for ½ hour.	Fever 1 day	8 days	3 days	Few days	Few days	3 weeks	2 days	6 days	5 days
Onset	Several days	Sitting in chair after shaving	Getting out of a car	Walking on street on cold day	In bed	Sitting in a train car	While wrestling.	Standing dribbling.	In bed 15 minutes after delivery
Sounds	Crunching, bubbling	Systolic, crunching	Loud, moist, crackling and crepitant systolic noise	Crackling sound with each systole	Crackling, clicking sounds varying with each systole	Crackling, popping sounds over the sternum	Hollow, knocking sound similar to that over brachial artery when taking B.P.	Heard across the room	Like wrinkling of a newspaper	Clicking, crunching, grating sound in chest and 2d and 3d left interspaces
Trepopnea	Sitting up	Sitting up	Right side	Flat on back
Decrease in cardiac dullness	0	0	Marked	Marked	0
Subcutaneous emphysema	0	+	0	0	0	+	+	0	Small transient over sternum	0
Electrocardiogram	Low potential, but otherwise normal	Low voltage in Lead II	Normal	Normal on 3d and 7th days
Intrathoracic sounds heard by patient	Synchronous with the heart beat	Synchronous with the heart beat	In region of the heart	Synchronous with the heart beat	Synchronous with the heart beat	In the region of the heart	0
Sounds heard best with patient	On left side	On left side. Disappeared on sitting up	Only with the patient flat on his back	Standing or sitting, absent with patient flat on back	In any position	In any position
Roentgen ray	N	N	Early infiltration at apices	Small left pneumothorax	Air in mediastinum between anterior chest wall and heart	Left pneumothorax	Small left pneumothorax	Air in mediastinum lateral view	Negative
Pneumothorax	0	0	0	Small, left	Small, left	0	Large, left	Small, left	Small, left	0

respects they are like the notoriously fickle pericardial friction rub after coronary occlusion. Apparently the break in continuity of the air passages may close temporarily and open again, allowing more air to escape into the interstitial tissues, thus producing changes in physical signs. Any increase in the sounds is apt to be associated with an exacerbation of the pain.

These cases may exhibit trepopnea and both patients in this report preferred to lie flat in bed. Since movement may increase the pain, the patients prefer to remain very quiet. Respiratory motions may be limited on the side where the pain is greatest. Such activities as coughing and sneezing may be agonizing and are strongly resisted.

In the first case there was complete obliteration of the area of cardiac dullness. Roentgen rays revealed a small collection of air between the heart and anterior chest wall and a small pneumothorax on the left. It may be of some significance that when pneumothorax has been encountered, it has been on the left side.

Subcutaneous emphysema was detected at no time in Case 2, though diligent search was made on repeated occasions. In the first case it would have been missed without repeated search, as it was very small in amount and had disappeared within 3 hours. Neither of the cases had air in the subcutaneous tissues above the clavicles.

Recently there was a patient on the medical wards in whom a not infrequent accident consequent upon thoracentesis gave confirmatory evidence to the suggestions made by Hamman regarding the pathogenesis of this condition. During the procedure the lung was punctured by the needle and a pneumothorax was induced. The patient soon called attention to a curious noise emanating from his chest. Slight pain was present in the chest. The sounds were audible to the naked ear 2 feet from the chest wall and on auscultation one could hear the typical grating, grunting and crunching sound, which was very loud. There was no subcutaneous emphysema and in 2 days the sounds were no longer to be heard. Roentgen ray confirmed the diagnosis of pneumothorax but did not reveal a mediastinal emphysema. This clearly illustrates that the signs appearing in spontaneous interstitial emphysema of the lung may be produced artificially by puncture of the lung. Such an event occurring spontaneously may give rise to nothing but a pneumothorax. We feel, however, that escape of air into the interstitial tissues of the lung is by no means rare and that if all cases with spontaneous pneumothorax were examined carefully, the typical sounds described above would be found frequently. In many cases, the patient calls the attention of the physician to the curious noises within the chest.

Differential diagnosis must be made between this condition and coronary thrombosis, pneumonia, pulmonary infarction and pericarditis. The finding of the unusual precordial sounds in a patient

with severe pain and the absence of other signs commensurate with the symptoms should lead one to make the diagnosis. Roentgen ray may reveal the air in the mediastinum, or subcutaneous emphysema may appear to substantiate it. Because of the benign nature of the condition, patients may be reassured and spared unnecessary invalidism.

Treatment should be conservative and palliative. Unless there is extensive subcutaneous emphysema, there is no reason to use 95% oxygen as advised by Fine, Hermanson and Frehling.²

Summary. 1. Two cases of Hamman's Disease (spontaneous interstitial emphysema of the lung) are described.

2. The syndrome results from the rupture of alveoli, or small bronchioles, the escape of air from its normal pathways within the lung, its dissection along interstitial bands and passage into the anterior mediastinum.

3. Criteria for the diagnosis are: Sudden onset of pain in the chest with bubbling, crunching sounds heard over the heart. Additional signs are: Decrease in the area of cardiac dullness, evidence of air in the mediastinum by Roentgen ray examination of the chest in the lateral position, and pneumothorax, especially of the left side.

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THE INCIDENCE OF THE VARIOUS TYPES OF GASTRIC DISEASE AS REVEALED BY GASTROSCOPIC STUDY.

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STATISTICS on the various types of gastric disease based solely on gastroscopic observations necessarily must have fundamental disadvantages. Not every patient suffering from epigastric distress is subjected to gastroscopy, even not if gastroscopy is considered to be a very important method of examination for these patients. This statement especially refers to duodenal ulcer. Usually gastroscopy is preceded by Roentgen ray, and by careful Roentgen ray relief study almost every duodenal ulcer can be demonstrated. If

by Roentgen ray examination the niche of a duodenal ulcer has been found, often gastroscopy may appear unnecessary. The same is true of some cases of gall bladder disease. Nevertheless, gastroscopy reveals many diseases which cannot be found by any other method. Therefore it seemed to us to be worthwhile to compile the findings of all patients examined with the flexible Wolf-Schindler gastroscope. Such a compilation not only gives an idea about the percentual distribution of gastric diseases, but also permits comparison of the incidence of gastric diseases in Europe (Munich) and in the United States (Chicago), since 335 gastroscopies in 255 patients were carried out in Munich, and 1691 gastroscopies in 1000 patients were carried out in the United States, most of them in Chicago.

Evidently the quality of such a material does not depend only upon geographical factors. Personal and occasional factors may play an important rôle. This is particularly true if low figures are used, and for this reason no statistical summary was attempted before 1000 patients had been examined gastroscopically.

The incidence of *acute* gastric disorders cannot be determined from gastroscopic observation, since there is no indication for gastroscopic examination in acute gastritis, in some forms (corrosive gastritis, phlegmonous gastritis) gastroscopy even being contra-indicated.

Lack of certain material may also influence the statistics. Alterations of the gastric mucosa probably are not infrequent in pulmonary tuberculosis; however, patients suffering from tuberculosis rarely are referred for gastroscopy. The same is true of colitis and appendicitis, although according to recent observations severe gastritis may be combined with these diseases (Royer, Bur, Montejano.⁶) Perhaps still more important is the lack of skin diseases, allergic diseases and certain blood diseases in our statistics. The French school, especially P. Chevallier and Moutier,² have shown that many kinds of alteration of the gastric mucosa occur in chronic skin diseases, such as eczema, urticaria, and others. It seems that atrophic gastritis in such conditions is frequent in accordance with older dermatologic conceptions. However, this type of disease is missing in our material. The same is true of gastric allergy. Allergic manifestations of the gastro-intestinal tract have often been assumed; their presence has been proved by careful gastroscopic observations by R. Chevallier.³ I have not had the opportunity to gastroscope patients suffering from allergic gastro-intestinal symptoms. In most blood diseases definite changes of the gastric mucosa are present, and our material contains many cases of pernicious anemia, but not many of severe secondary anemia or leukemia.

Some gastric diseases are so rare that they are not encountered even in 1000 patients, as for instance, gastric tuberculosis, anthrax and actinomycosis. Finally there may be gastric disease without

gastric symptoms. We have reason to believe that diffuse atrophic gastritis may have general symptoms such as tiredness, weakness, and so on, rather than gastric symptoms, and that therefore such patients are not subject to gastroscopy.

Race of the patient does not seem to play a great rôle. In immigrants of all European nations the same diseases were found. Our experience with members of the colored races is not yet extensive enough to permit a definite statement.

One thousand patients were examined in the United States; 733 of them were referred by the various departments of Billings Hospital, University of Chicago, the majority from the gastro-intestinal service of Dr. W. L. Palmer. About two-thirds of them were out-patients. None of them was hospitalized for the gastroscopic examination. One hundred and eighteen patients were examined at Cook County Hospital, Chicago, all of them being in-patients. The same number (118), were examined at Michael Reese Hospital, Chicago, most of them being out-patients; 17 colored patients were referred by the Gastro-intestinal Department (Dr. L. Berry) of the Provident Hospital, Chicago; 6 patients were examined at the Cincinnati General Hospital (Dr. Leon Schiff), 4 patients were examined at the Indianapolis General Hospital (Dr. M. Light), 3 at Oak Forest, Illinois (Dr. J. Eisemann), and 1 at St. Mary's Hospital, Chicago.

In the following table the incidence of the diseases found has been listed. Often several diseases were found in 1 patient. In these instances the case was classified under that disease which usually is considered to be the chief disease. For instance, cases in which ulcer plus gastritis or carcinoma plus gastritis or ulcer plus pigment spots were found were classified as ulcer or as carcinoma respectively (Table 1).

Comment. 1. Under the heading "*Normal stomach*" are included: Psychoneuroses, cases of duodenal ulcer without visible inflammatory or circulatory changes, gall bladder diseases and other organic diseases. The number of these cases is not known.

2. Hemorrhages lying in a normal mucosa cannot be classified under inflammation, as I have repeatedly pointed out. The mucosal hemorrhages seen in generalized purpura are entirely similar to those found in ulcer-bearing stomachs or otherwise lying in a normal mucosa sometimes combined with pigment spots or hemorrhagic erosions. Therefore, we have classified these three phenomena as "localized gastric purpura." In 1 case profuse gross gastric hemorrhage was observed.

3. Most *gastric ulcers* were observed over a period of months or years by repeated gastroscopies (up to 28). A few gastric ulcers demonstrated by Roentgen ray were not found gastroscopically. If they would be added, the total incidence of gastric ulcers would rise to about 7.7%.

4. *Sequelæ of ulcer* are called: benign obstruction of the pylorus,

scars, formation of hour-glass stomach, and perigastric adhesions, the latter being proved by distortions of the stomach and other alterations of shape.

5. There are probably two different entities of *chronic non-specific gastritis* which should be listed separately: the superficial-atrophic form and the hypertrophic form.

TABLE. 1.—INCIDENCE OF GASTRIC DISEASES AS FOUND BY GASTROSCOPIC EXAMINATION OF 1000 PATIENTS IN THE UNITED STATES.

	Percentage.	Number of patients.
Normal stomach	22.2	222
Mucosal hemorrhages, pigment spots and hemorrhagic erosions of non-inflammatory origin (localized gastric purpura)	5.6	56
Gastric ulcer	7.1	71
Sequelæ of gastric ulcer	1.4	14
Chronic non-specific gastritis:		
(a) Chronic superficial gastritis	11.0	
(b) Chronic atrophic gastritis	13.6	
(Superficial plus atrophic gastritis)	24.6	
(c) Chronic hypertrophic gastritis	17.2	
Total chronic non-specific gastritis	41.8	418
Gastric syphilis	0.3	3
Gastric lymphogranuloma (Hodgkin's disease)	0.2	2
Benign tumors	2.2	22
Gastric carcinoma	7.7	77
Lymphoblastoma	0.1	1
Congenital diverticula	0.3	3
Diaphragmatic hernia	0.2	2
Postoperative stomach	8.0	80
Accidents	0.3	3
Examinations attempted, but not successful	1.4	14
Examinations made, but not satisfactory	1.2	12

a. Three of the 110 cases of *superficial gastritis* were seen in duodenal ulcer, 3 in cholangitis, 4 followed therapeutic Roentgen ray irradiation (high voltage Roentgen ray therapy); 1 case was observed in alcoholic pellagra. Five times the diagnosis of a superficial *hemorrhagic* gastritis was made, five times that of superficial *erosive* gastritis, and five times that of superficial hemorrhagic erosive gastritis. A superficial *aphthous* gastritis combined with aphthæ of the mouth was seen in 2 instances. In this series no gross hemorrhage occurred in superficial gastritis.

b. Under "*Atrophic Gastritis*" also those cases were classified which showed a combination of superficial with atrophic changes. In 38 of the 136 cases of atrophic gastritis, superficial gastritis was also present. The frequency of this combination proves the close relationship between these two conditions. They constitute together Faber's chronic progressive pangastritis. Of the cases of atrophic gastritis 15 were seen combined with pernicious anemia, 1 combined with cord degeneration, and 1 combined with tropical sprue. One case of atrophic gastritis was observed in a patient suffering from duodenal ulcer, 2 in patients suffering from cholecystopathy, 1 in a patient who had had lymphatic leukemia, 1 combined

with tuberculosis of the lungs, and 1 combined with acute appendicitis. In 13 cases an atrophic hemorrhagic gastritis was found; but in only 3 instances were *erosions* seen. One atrophic erosive gastritis was found in the patient who suffered from acute appendicitis. In 2 instances severe *gross hemorrhage* was observed.

5. Chronic *hypertrophic gastritis* probably is a clinical entity, although some cases may be related to the atrophic type. In 11 of the 172 cases the diagnosis of hemorrhagic hypertrophic gastritis was made, indicating that mucosal hemorrhages were seen gastroscopically. In 12 cases *ulcerations* of the inflamed mucosa were observed and consequently the diagnosis of ulcerative hypertrophic gastritis was made. In 5 instances hemorrhages plus ulcerations were seen. Four times *gross hemorrhage* was found to originate from hypertrophic gastritis; in 1 of these cases continuous parenchymatous oozing of blood was observed gastroscopically. Ten cases were found in patients suffering from duodenal ulcer, 1 case, respectively, in a patient with lymphogranuloma inguinale and uremia.

6. The diagnosis of gastric *syphilis* was made when *a*, an inflammatory or tumor-like thickening of the gastric mucosa with or without formation of ulcerations was observed gastroscopically; *b*, the Wassermann test was strongly positive, and *c*, the changes observed disappeared after antiluetic treatment.

7. A tremendous thickening of all folds was found in 1 case of *Hodgkin's disease*, while the second one presented the picture of ulcerative hypertrophic antrum gastritis.

8. In 20 instances the *benign tumors* were considered to be epithelial tumors, probably benign adenomas. In 3 cases they were found in pernicious anemia; in 2 instances severe gross hemorrhage—apparently due to the polyps—was observed. In 2 cases the appearance of the tumor was that of a submucosal one, probably of a myoma. Both patients were referred for gastroscopic examination because of gross hemorrhage.

9. Carcinoma of the stomach was usually found easily gastroscopically except, *a*, the case in which obstruction at the cardia rendered examination impossible; *b*, 1 case in which hour-glass formation and 1 in which invagination through an enterostomy stoma prevented visualization of the lesion; and *c*, 2 cases of extensive scirrhus carcinoma in which little could be seen, although the diagnosis could be made because of the lack of distensibility of the stomach. This good result contrasts with the results of other gastroscopists. Important information was obtained bearing on the macroscopic type of tumor and upon its operability. Borrmann's¹ simple classification of gastric carcinoma according to their macroscopic appearance has been proved to be valuable. The very favorable, sharply limited polypoid Type 1 carcinoma was found in only 2 instances. The Type 2 carcinoma, the localized malignant ulcer, surrounded by a sharply limited wall, was encountered 12 times. The Type 3 carcinoma gives a very dubious prognosis; it is a malig-

nant ulcer, walled off only on one side of the ulcer; it was seen in 11 cases. The unfavorable diffusely infiltrative Type 4 carcinoma was observed in 43 instances. In 5 cases a carcinoma of the cardia was visualized gastroscopically. Gastroscopy proved to be especially valuable in differentiating benign and malignant ulcers. In 3 of the 77 cases gastroscopically examined, a carcinoma was diagnosed at a time at which clinically and roentgenologically a benign ulcer was believed to be present. In all 3 cases the Roentgen ray niche apparently became smaller under treatment, but in every instance operation or autopsy proved that the gastroscopic diagnosis had been correct.

10. The case of *lymphoblastoma*, the third to be observed gastroscopically, has been described by Renshaw.⁴

11. Two of the 3 *congenital diverticula* observed occurred in syphilitics. They had, however, the outspoken appearance of a congenital lesion.

12. *Hernia Diaphragmatica*. At two examinations the gastro-scope entered the stomach. One of the 2 patients was examined repeatedly, but usually only the supradiaphragmatic portion of the stomach became visible.

13. Gastroscopy was carried out in 29 resected stomachs, in 50 patients having a gastroenterostomy, and in 1 patient having had a pyloroplasty. In this latter, a gastritis of the postoperative stomach was found. In the other groups, the findings were as follows:

Resected Stomach. An entirely normal stomach was found in 3 instances. In 2 of them the stoma showed the rare picture of rhythmical pylorus-like contractions. (We should not forget that usually only patients suffering from distress were observed). In 2 instances mucosal hemorrhages of the normal mucosa were found (virtual ulcer stomach, see p. 511). Jejunal or marginal ulcers were found in 4 cases, but no recurrent ulcers were seen in the stomach proper in this group. Gastritis of the postoperative stomach was found in 16 instances, jejunitis plus gastritis twice. Recurrent carcinoma was present in 2 cases, but visible only in 1 of them.

Gastroenterostomy. The stomach was found to be normal in 6 instances, in 3 of which rhythmical function of the stoma was observed. In 1 case mucosal hemorrhages of the normal mucosa were seen. Jejunal and marginal ulcers were seen 5 times, recurrent gastric ulcers twice. In 1 case, obstruction of the jejunum below the opening was diagnosed from the rhythmical ejection of white bismuth powder through the stoma from the intestine into the stomach. This diagnosis was confirmed by operation. Silk sutures (always combined with gastritis or erosions) were seen in 4 cases. Gastritis was found 30 times. A gastro-colic fistula was present once. The old opinion of all gastroscoping clinicians that a severe gastritis is the most important disease of the postoperative stomach was confirmed.

14. The three *accidents* occurring with the flexible gastroscope

have been described elsewhere. They were non-fatal perforations of the gastric wall and they happened within a very short period of time, during gastroscopies Nos. 713, 771 and 781 (June 30, 1935 to September 12, 1935). It was possible to prove experimentally⁸ that they were due to a modification of the standard tip of the gastroscope, the so-called "rubber-sponge." Since returning to the use of the rubber finger tip, there have been no accidents to date in over 1323 examinations.

15. *Examinations attempted but not successful* include those in which the attempt of a gastroscopic examination was made, but did not succeed. The reasons thereof were: Non-coöperation of the patient, 5 times; unexpected lesions of the cardia, 8 times; food remnants, once.

16. *Examinations made but considered unsatisfactory* were those in which the introduction of the gastroscope was possible, but important portions of the stomach, especially its distal parts, were hidden from view. The reasons (12 cases) were: Non-coöperation, 3 times; continuous spasms, once; obesity, once; food in the stomach, twice; barium in the stomach, twice; distention of the stomach impossible because of leather-bottle formation, once; distortion of the stomach from adhesions, once; kyphosis, once.

Finally, diagnostic errors must be considered. No diagnostic method probably is free of the possibility of error. And if errors are frequent they may influence the statistical results. The number of mistakes in gastroscopy depends largely upon the experience of the examiner. To the best of our knowledge the following mistakes were made: Six ulcers located in the so-called blind areas of the stomach were not found. These are not "wrong diagnoses," since knowledge of the gastroscopic method presupposes the presence of these blind areas and assumes that localized lesions of these areas cannot be found gastroscopically. Perhaps this disadvantage can be diminished by further development of the method (Rodger's sheath.⁹) One carcinoma of the postoperative stomach was not seen because of overlapping invaginated mucosa. In 1 case a hemispherical protuberance of the antrum was described; autopsy in this case revealed a carcinoma of the pancreas. In 2 cases the differential diagnosis between infiltrative carcinoma and hypertrophic ulcerative antrum gastritis was impossible. In 1 of them, in which I was inclined to diagnose a carcinoma an antrum gastritis was found, in the other 1 antrum gastritis seemed to be more likely, but carcinoma was found. Possibly other mistakes were made which were overlooked, in spite of the attempts to check every case. Therefore, no figure for wrong diagnoses can be given.

It has been contended that the incidence of gastric diseases in Germany differs from that in the United States (Walters and Sebening⁹). Therefore, German statistics shall be given, though based on a smaller material. In a specialized gastro-intestinal practice in Munich 335 gastroscopies were carried out in 255 patients from

1932 to 1934. The Wolf-Schindler flexible gastroscope was used. The findings are given in Table 2.

TABLE 2.—INCIDENCE OF GASTRIC DISEASES AS FOUND BY GASTROSCOPIC EXAMINATION OF 255 PATIENTS IN GERMANY.

	Percentage.	Number of patients.
Normal stomach	24.3	62
Mucosal hemorrhages, pigment spots and hemorrhagic erosions of non-inflammatory origin (localized gastric purpura)	8.25	21
Gastric ulcer and sequelæ of ulcer	8.6	22
Chronic non-specific gastritis:		
(a) Chronic superficial gastritis	12.0	
(b) Chronic atrophic gastritis	19.0	
(Superficial plus atrophic gastritis)	31.0	
(c) Chronic hypertrophic gastritis	14.0	
Total chronic non-specific gastritis	45.0	115
Benign tumors	1.6	4
Carcinoma	7.85	20
Postoperative stomach	3.2	8
Examinations attempted, but not successful	0.8	2
Examinations made, but not satisfactory	0.4	1

The difference between the two statistics is so slight that it almost is unnecessary to discuss it. However, although the proportion of chronic gastritis is about the same in Munich as in Chicago, the distribution of the two great groups is a different one: In Chicago the percentage of superficial-atrophic gastritis is 24.6%, in Munich 31%. In Chicago hypertrophic gastritis is 17.2%, in Munich 14%. No cases of ulcerative antrum gastritis were seen in Munich. The incidence of "localized gastric purpura" was higher in Munich than in Chicago (8.25% to 5.6%). The ulcer figures (8.5% to 8.6%) and the carcinoma figures (7.7% to 7.85%) were about the same. The higher incidence of postoperative stomachs in Chicago is noteworthy (8.0% to 3.2%). The smaller figure of impossible and unsatisfactory examinations in Munich is easily explained by the fact that in Munich all patients were private patients seeing the doctor of their own choice and therefore being confident and quiet.

Summary. 1. Statistics on the incidence of gastric diseases in the United States and in Europe are presented, based upon gastroscopic findings in 1000 and in 255 patients.

2. There are apparently no outspoken geographical differences in the distribution of gastric diseases.

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A REVIEW OF A FIVE-YEAR TUBERCULOSIS PROGRAM AMONG UNIVERSITY OF WISCONSIN STUDENTS.

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QUOTING from the 4th verse of the 16th chapter of St. Matthew—"A generation seeketh after a sign and no sign shall be given unto it"—the proposition as concerns disease and especially tuberculosis in its early stages is well expressed. For many centuries pulmonary tuberculosis has been associated with certain common and well known symptoms. Considering early diagnosis this association has been unfortunate, for usually the minimal and not infrequently the moderately advanced stages occur without symptoms. Even the far advanced stage has not produced symptoms sufficient in degree to prevent 4 students—unaware of their active tuberculosis—from enrolling in the University during the past 5 years. The association of symptoms and tuberculosis offers an adequate explanation why, according to a recent survey (1935) of the American Medical Association,¹ only 13.1% of 66,861 patients were admitted to sanatoriums in the minimal stage, while 29.7 and 57.2% respectively were in the moderately advanced and far advanced stages. Compared to the earlier surveys by Drolet⁵ (1926) and Whitney⁷ (1931), no progress as regards earlier diagnosis has been made. Because treatment early in the disease is undoubtedly the biggest factor in recovery, it is unfortunate that late diagnoses are still the rule. An efficient and well directed tuberculosis program would make possible the discovery of more than 70% of all cases while still in the minimal stage. Today, unfortunately, and of necessity, the time and energies of sanatorium physicians must be directed to caring for the large proportion of patients who have far advanced tuberculosis—cases which emphasize the futility of treatment late in the disease.

Medical practice in the past has been hampered by the lack of a general public interest in health and medical efforts for its maintenance. Without the technical assistance of Roentgen ray and the laboratory, physicians necessarily had to be content to study the pathologic process after it had reached a stage sufficient to produce symptoms and clinical signs. Usually in the study of pathologic processes we first learn and recognize disease in its late or end stages as presented at the bedside or postmortem table, and relatively speaking know little of the manifestations of early disease when treatment is most effective. Since the presence of early disease can be determined in many instances only by laboratory means, it is evident that the methods of approach must change. With a rapidly growing appreciation by the layman of the value of disease

prevention and earlier discovery, the importance of an annual medical examination will be more widely recognized. This offers the physician a great opportunity, and he should not be content to let this important examination consist of a physical examination and a pat on the back with the assurance that everything is all right. Good medical practice in the future will demand more. Urine analysis will consist of more than the examination of a single specimen. Urine collected during a 24-hour period will be examined for sugar, albumin, pus and blood. Chemical analysis of the blood for sugar will be done to diagnose diabetes not yet severe enough to cause symptoms. Laboratory tests can determine the function of the kidneys and the heart, and Roentgen ray examinations of the teeth, sinuses, bones and lungs will in many instances discover disease not known to exist. Special examinations of the gastrointestinal tract frequently would reveal latent disease, and microscopic examination of tissues might prove or disprove a diagnosis. Today we make little effort to find a pathologic process until it produces symptoms, and, therefore, have much to learn as to the origin and pathogenesis of early disease. When the apparently healthy present themselves for study, the medical profession should be sufficiently informed and interested to give an adequate health examination.

A student health department, dealing with apparently healthy individuals, is at once met with the challenge as to whether all individuals matriculating in college are in fact healthy and physically capable of carrying the burden of a college course. Allowing a student with a clinically latent but pathologically active disease process to do his work without close medical supervision is obviously dangerous. In the past, health examinations have consisted primarily of a history, physical examination and a single examination of the patient's urine. That with further special studies much more can be determined as to the student's status is well illustrated by this survey of pulmonary tuberculosis—a disease frequently found among the college age group.

Tuberculous Infection. The diagnosis of minimal pulmonary tuberculosis is dependent on repeated examination of the apparently healthy for tuberculous infection and disease. The success of dairymen in many states in reducing infection among cattle to less than 0.5% suggests the value of a similar effort among humans. Much money and energy has been and is being expended in treating the 87% with moderately and far advanced disease. Relatively little has been done to find and treat the process while it is still in the minimal stage. The potentialities of a tuberculosis program to include the general population are suggested by the results of a 5-year survey among University of Wisconsin students.

All students enrolling for the first time in the University are given as part of their entrance health examination a tuberculin test.

Those showing no reaction to 0.005 mg. of standardized tuberculin (Purified Protein Derivative of Seibert and Long) are regarded as free of tuberculous disease* and in most instances of tuberculous infection. To date, no case of pathologically active tuberculosis has been discovered in an individual having a negative Mantoux test to 0.005 mg. P. P. D. or to 1.0 mg. Saranac Lake Laboratory Old Tuberculin. During the 5-year period over 16,000 students have enrolled in the University for the first time. Students enrolling in September totaling over 15,000 have been tested by the 2-dose method. A smaller group numbering over 1000 enrolling at the beginning of the second semester were tested with the single stronger dose—0.005 mg. P. P. D. It was found that with the 2-dose method, the total percentage of 3 and 4 + reactors was 3.7 and 0.24% respectively, compared to 8.6 and 1.5% when the single strong dose was used. Otherwise stated there were 2.3 times as many 3 + reactors and 6 times as many 4 + reactors when the single strong dose was used. Though no ill effects other than a very sore arm, accompanied in certain cases by constitutional symptoms, have been noted, the 2-dose method is preferable. If only one dose of tuberculin is given, the examiner should appreciate the fact that unless the stronger strength dose is used—either 0.005 mg. P. P. D. or 1.0 mg. O. T., all active cases of tuberculosis will not be found. Of the 71 active cases discovered in the 5-year period, 16 (22.5%) failed to react to the weaker dose. Of the 16 not reacting to the weaker dose, 5 had suspicious positive reactions to the first test, but without edema approaching 5 mm. The single strong dose method is not advocated; but since in many case finding programs the single weak dose alone is used, the fact should be emphasized that by this method in our study only 57% of the infected would have been determined, and all of the active cases would not have been found. Where the 2-dose method was used, 16.23% (57% of total positive) reacted to the first strength P. P. D. and an additional 12.24% (43% of total positive) reacted to the stronger dilution.

Where large numbers are concerned, the yearly increase of infection in the age groups from 16 to 25 is shown in Table 1. The possible reasons for the rapid increase from 19.4% to 50% in this 10-year period are of interest. Certainly in this stage of life the individual leaves his rather limited home circle. His acquaintances and contacts increase, he covers a wider geographic range; and his social habits further the possibility of infection. The frequency with which tubercle bacilli are found in minimal tuberculosis by special examination^{6c} suggests that these asymptomatic cases may be infectious to others by kissing or mouth to hand contact.

Summaries of the Mantoux tests by ages (Table 1) indicates a con-

* Roentgen ray study of a group of students negative to 0.005 mg. P. P. D. revealed that 6% had calcified lesions in the lungs or hilum glands.

sistently smaller infection rate among women. The total number of infected, though showing a yearly variation of only 2.75% in the years 1933 to 1936 inclusive, with an average yearly infection rate of 28.5%, showed a marked decrease in 1937 to 23.3%. Whether the most recent figure will serve as an indicator pointing to a lower infection rate in the future will be of notable interest.

The geographic variation of infection among students from different sections of the country is shown in Figure 1. The higher infection rates of students coming from the East are consistent with

TABLE 1.

TUBERCULOUS INFECTION
MANTOUX TESTS OF 16,109 STUDENTS
FIVE YEARS 1933-1938

AGE	NO TESTED	PERCENT + WOMEN	MEN	TOTAL POSITIVE	
10-15	106	11.9	172	119	PERCENT
16	139	18.5	197	194	
17	1438	18.9	219	203	
18	4735	19.5	224	212	
19	3240	21.2	249	236	
20	2130	26.6	266	266	
21	1324	25.8	351	328	
22	922	29.4	429	35.2	
23	514	44.3	382	39.1	
24	392	43.8	400	41.1	
25	234	44.0	546	50.0	
26-30	591	44.3	542	50.6	
31-35	203	61.7	689	66.0	
36-40	89	58.1	652	61.8	
41-45	32	94.1	867	90.6	
46-50	11	71.4	100	81.8	
51-55	9	80.0	100	88.9	
TOTALS	16,109	24.1%	29.5%	27.6	

WOMEN TESTED 5,608
MEN " 10,501

*PPD WAS USED IN ALL BUT 1987 STUDENTS TO WHOM SARANAC LAKE OT. WAS GIVEN
FAILURE TO REACT TO 10 mg OT OR 0005 mg PPD CONSIDERED NEGATIVE*

the infection rates found in Eastern colleges.² Only the mountain states approximate the low infection rate of the north central area. The high infection rate of Arizona and New Mexico is indicative of the probability of infection of those living with the tuberculous. Two University of Wisconsin students, spending a winter in Tucson, Arizona, negative on leaving, were positive on return. Infection rates among students from the Southeast are uniformly high, and approach the rates of those from the East.

As to infection rates among urban and rural groups, it is of interest to note that of all students tested, those coming from rural Wisconsin and enrolled in the short course in Agriculture show the smallest

incidence of infection. Of 742 students tested, 175 (23.6%) were positive. In no instance to date has a case of pathologically active tuberculosis been found in this group.

Though the numbers are not large and, therefore, offer no proof, they suggest a correlation between the infection rates of students and the death rates of the county or section of the state from which they come. Infection by counties is presented in Figure 2. The Wisconsin tuberculosis death rate per 100,000 population for the 8-year period from 1930 to 1937 was 41.8.* Of Wisconsin's 72 counties, 13 have death rates above the state average. The northern-

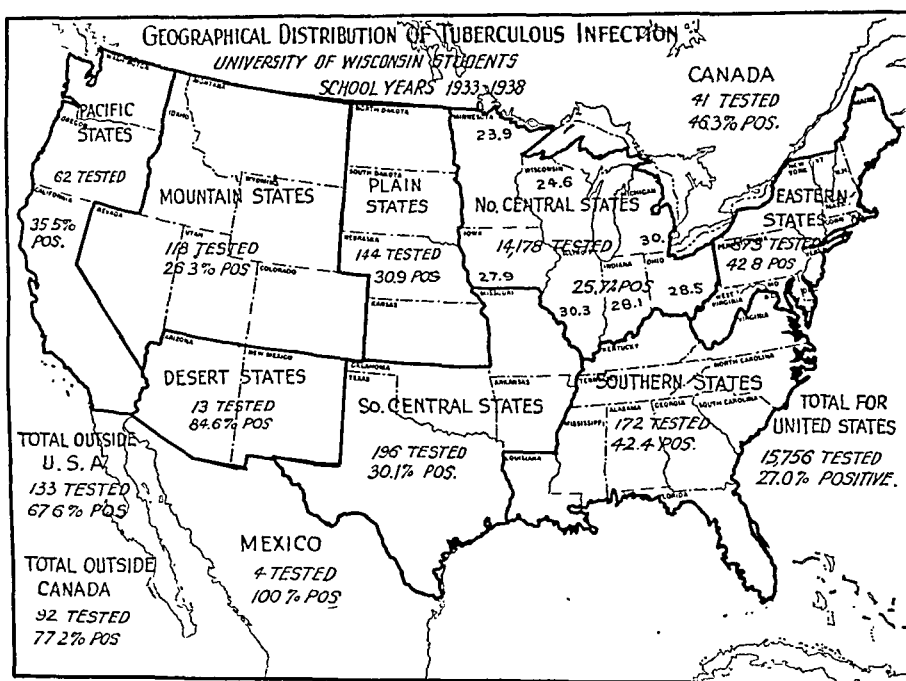


FIG. 1.

most tier of counties, 8 in number, and 2 counties adjacent contain 10 of the 14 counties having the highest death rates in the state. No other combination of an equal number of Wisconsin counties has such a high infection rate as these 10 northern counties. The most heavily populated areas of the state, Milwaukee, Racine and Kenosha counties, also show a high infection rate. The death rate of Milwaukee County ranks seventh among the counties, while the rates of Racine and Kenosha counties are below the state average. The high infection rates of Winnebago and Jefferson counties from which relatively large numbers of students were tested cannot be explained on a basis of death rates.

* Statistics of the Wisconsin Anti-Tuberculosis Association and Wisconsin State Board of Health.

by the first infection. The non-infected have not established their status. From evidence at hand it appears that progressive tuberculosis may develop from the first infection. Close observation of the pathologic process following the known time of infection will alone answer the question.

Myers and his co-workers⁴ are of the opinion that the first infection occurring in either childhood or adult life is benign and requires no treatment. Some of their conclusions follow:

"The first infection type of tuberculosis as observed in our group of adults has resulted in no significant symptoms or abnormal physical signs throughout the entire course of development. Indeed the lesions in the majority of our cases would not have been known to exist had it not been for periodic tuberculin testing and the making of Roentgenograms of the positive reactors.

"In our experience, adults in whom the first infection type of tuberculosis develops, even with considerable involvement in the pulmonary parenchyma and regional lymph nodes, do not require treatment in any form.

"Apparently it makes little or no difference at what time of life the first infection with tubercle bacilli occurs, with reference to the evolution of tuberculosis in the human body. When the first infection type of disease occurs in the second and third decades of life, it is just as benign as when it occurs in childhood."

Our experience in 4 cases of students recently infected has been very different from that of Myers. Two students developed cavitation from lesions, as indicated by the sequence of events, resulting from first infection. Both subsequently developed symptoms and physical signs, and after 1 and 2 years of treatment respectively are still in sanatoriums. Another, after 2 years of treatment returned to the University this past semester, and tubercle bacilli continued to be present in her gastric contents, though her pulmonary lesion had receded in size. A student nurse formerly repeatedly negative to tuberculin became infected during the past few months, and showed definite progression of a subclavicular lesion during a month's observation. Because of the experience with the other 3 cases in which benignity did not prevail, treatment of this lesion resulting from first infection has been instituted. The fact that only a relatively small per cent of the total infected develop progressive tuberculosis from the first infection does not justify the conclusion that first infection tuberculosis is always benign and does not require treatment.

Because of the multiple factors involved in determining the course that a tuberculous pathologic process will take, be it either from a first or reinfection, it may be questioned whether there is sufficient justification in stating which produced the lesion, a first infection or reinfection.

Tuberculin Retests. Students failing to react to the tuberculin test on entrance to the University are requested to report for a retest each year. Of a total of 1806 retested in January, 1937, 1610 (89%) reported for a reading of their arms. Of this number, 83 (5.2%) were positive. The 196 who failed to report for interpretation of their test were probably negative, for students by receiving a yearly test soon learn to interpret a negative result, and knowing its meaning neglect to report. This would lower the rate of infection per year to 4.6%. A more complete statistical compilation of the results of retesting done in January, 1938, is indicated in Table 2. Of 2023 retested, 1829 (90%) reported for interpretation of their test. Assuming again that the 194 who failed to report had negative tests, the rate increase of infection per year would be 4.1%.

TABLE 2.—ANNUAL MANTOUX RETESTS, JANUARY, 1938.

Year enrolled.	Summoneed.	Reported.		Men.						Women.						Men and women.		
				Summoneed.	Reported.		Pos.		Summoneed.	Reported.		Pos.		Tested.	Pos.			
		No.	%		No.	%	No.	%		No.	%	No.	%		No.	%		
1933	264	108	41.0	248	94	37.9	6	6.4	16	14	87.5	1	7.1	108	7	6.5		
1934	735	289	39.3	532	211	39.7	9	4.3	203	78	38.4	3	3.8	289	12	4.1		
1935	1305	585	44.1	877	425	48.4	31	7.3	428	160	37.4	2	1.3	585	33	5.6		
1936	1792	847	47.2	1153	554	48.0	23	4.2	639	293	45.9	7	2.4	847	30	3.5		
Total	4096	1829*	44.6	2810	1284	45.7	69	5.3	1286	545	42.4	13	2.4	1829*	82	4.5		

* A total of 2023 were tested, of which number 1829 (90%) reported for reading of test.

Since individuals showing erythema and edema measuring less than 5 mm. and who are considered negative at the time of enrollment, may in fact be infected³ and show a 1 or 2 + reaction when retested, it is probable that the figures of 1937 and 1938 of 4.6 and 4.1% respectively represent a figure slightly higher than the actual rate of increase of infection. Of special interest is the fact that rate of increase of infection among women is only 2.4% as compared to 5.3% among men. This is consistent with the lower infection rate noted in women in all age periods. The 10-year age period 17 to 26 inclusive in which the largest number were tested, showed that of 9326 men tested 27.8% were positive, while of 4874 women tested 22.4% were positive. The differences in habits of the opposite sexes (wider social contacts of male) probably accounts for the higher rate in the male.

Roentgen Ray Study. Students having positive tuberculin tests on entering the University and those who subsequently become positive to the yearly retest receive a single postero-anterior roentgenogram of the chest. Those showing no evidence of past lesions on the Roentgen ray are reexamined at 12 to 18-month intervals

by means of the fluoroscope. In trained hands the fluoroscope is an economical and efficient means of discovering tuberculosis. Where an infiltration or suspicion of an infiltration exists, roentgenograms of the lungs are requested. In individuals of average build, there is little difficulty in making the lesion visible. Because the patient's position is constantly being changed during the fluoroscopic examination, lesions lying well out in the periphery or obscured by the upper vertebral trunks, heart or diaphragm are brought into view. Better subsequent study by film is possible, because the examiner can request that a film be taken in the position in which it can best be seen. A small lesion may occasionally be obscured by the clavicle, or some other portion of the bony framework which on fluoroscopy, because of frequent position change, is easily enough brought into view. Additional advantages lie in viewing the excursion of the ribs, diaphragm and the mediastinum in both the lateral and oblique positions. Such routine study is not economically justifiable with films.

Differentiation between calcified deposits and blood-vessels outside the hila is readily possible by fluoroscopy. To date, individuals with calcified lesions have been reexamined more frequently than those without such deposits, but the necessity of such procedure should be questioned. Our experience indicates that parenchymal lesions developing while in college occur in greater numbers among those without calcification. Of the 71 cases of pathologically active pulmonary tuberculosis during the 5-year period, only 12 (16%) showed evidence of calcium in the lungs or hila. In only 8 was the calcification separate and distinct from the parenchymal lesion. It would appear, therefore, that more frequent examinations are indicated among the infected showing no calcification than among those who do. Possibly in the future we may find that the ability to calcify is an index of tissue resistance.

The roentgenogram examination of 4216 students who were found to be infected by the Mantoux test is presented in Table 3. It will be noted that the classification is divided into 3 groups, namely, no Roentgen ray evidence of pulmonary tuberculosis, calcified tuberculosis and non-calcified parenchymal tuberculosis. No attempt is made to indicate whether the lesion is a primary (childhood type) or reinfection (adult type) tuberculosis.

Without the knowledge that the individual was formerly always negative to a properly administered Mantoux test to a dose of 0.005 mg. P. P. D., or its equivalent of O. T., the contention is held that one cannot with any degree of accuracy tell from the Roentgen ray film alone whether the lesion visible resulted from a first infection or reinfection. Clinical observation supports this contention. Of a group of 15 girls^{6b} living in a rooming house with a sputum positive case for a period of 5 months, there were 11 who were known to have been negative to 0.005 mg. P. P. D. immediately previous to

exposure. All excepting one became infected. Two of these girls, recently infected, developed within 8 months of their exposure, subclavicular parenchymal lesions, typically so-called adult in type, which were undoubtedly progressive lesions resulting from their first infection. In another instance, a student having a positive tuberculin test was found to have a soft parenchymal lesion in the right second anterior interspace. Undoubtedly, by our present standards the lesions would have been classified as adult tuberculosis. Viewing the lesion 3 years later, marked contraction with calcification had occurred. The examiner not knowing the films were those of the same patient might now call the lesion a primary or childhood type. Recently (May, 1938) 2 girls, 1 a student nurse, both negative to 0.005 mg. P. P. D. in January, 1938, and on 2 previous occasions, developed pulmonary tuberculosis. In the student nurse a soft right subclavicular infiltration 1 cm. in diameter was found by routine fluoroscopic examination done on all student nurses at 6-month intervals. The other student, an employee in a hospital, complained of chest pain and was found to have a pleural effusion. Her tuberculin test, negative in September, 1936, and in January, 1938, was now strongly positive. The lesions in both girls are undoubtedly progressive processes resulting from their first infection contracted in the preceding weeks. From the evidence unfolding itself in the study of early tuberculosis, it appears that without proof of when infection has occurred, distinction as to whether a lesion resulted from a first or reinfection is not possible or justifiable and should not be attempted.

It will be noted in Table 3 that the percentage of negative films, calcified tuberculosis and parenchymal tuberculosis is expressed for both the infected and the entire student body (the latter group includes the infected). The fact is appreciated that some of the non-reactors to tuberculin are in fact infected, and a certain number would show, if Roentgen-rayed, lesions of healed and usually calcified tuberculosis (footnote p. 519). This number, however, is small; and in no instance to date has an active case of tuberculosis been found among those failing to react to 0.005 mg. P. P. D. The necessity of reexamination is emphasized by the fact that more cases of tuberculosis were proven active or developed subsequent to admission than were found at the time of enrollment, the ratio being approximately 3 to 2. The frequency with which infiltrations develop in lungs formerly normal by Roentgen ray emphasizes the importance of repeated examination. Of interest and significance is the fact that although the total incidence of tuberculosis among women enrolled is very slightly less (because of a lower infection rate), the incidence of active tuberculosis among the infected women is more than among the infected men—1.80% to 1.63%.

Table 4 represents roentgenogram studies by years. Because new cases are constantly developing, repeated revisions of the figures

are necessary. The group enrolling in the most recent school year shows the smallest per cent of active cases, but as new cases will be found during the coming years the number of active cases will probably approach the per cent of the preceding groups.

TABLE 3.—ROENTGENOLOGIC EXAMINATIONS.

Total Men and Women.

September, 1933, through February, 1938.

Total number positive Mantoux tests using Old Tuberculin and Purified Protein Derivative . . .	4447		
Number receiving roentgenologic examination . . .	4216		
Per cent of positive reactors receiving roentgenograms . . .	94.8%	Percentage of those receiving roentgenograms.	Percentage of total number of students receiving tuberculin test which numbered 16,109.*
Number with no Roentgen ray evidence of pulmonary tuberculosis . . .	3003	71.3	91.0 (14,665)†
Number with calcified lesions . . .	1022	24.2	6.3
Number with non-calcified parenchymal lesions . . .	191	4.5	1.2
Number of positives not receiving roentgenograms—231			1.4
	4216	100.0	100.0
Number of active lesions found active on enrollment . . .	29	0.69	0.18
Number of lesions proven active or developing subsequent to enrollment . . .	42	0.99	0.26
	71	1.68	0.44

* These figures are determined by assuming that all negative reactors would show no tuberculous lesion on Roentgen ray.

† This figure is determined by subtracting total number of positives from total tested and adding the number with no Roentgen ray evidence of tuberculosis.

TABLE 4.—ROENTGENOGRAM STUDY BY YEARS.

School year.	Roentgen-ray exams.	Negative films.		Calcified lesions.		Parenchymal lesions.		Pathologically active parenchymal lesions.	
		No.	%	No.	%	No.	%	No.	%
1933 . . .	529	374	70.7	128	24.2	14	2.6	13	2.5
1934 . . .	751	518	70.0	189	25.2	32	4.2	12	1.6
1935 . . .	953	676	70.9	240	25.2	22	2.3	15	1.6
1936 . . .	1091	760	69.7	281	25.8	29	2.7	21	1.9
1937 . . .	892	675	75.8	184	20.6	23	2.5	10	1.1
Total . . .	4216	3003	71.22	1022	24.24	120	2.84	71	1.68

TABLE 5.—TIME OF OCCURRENCE OF ACTIVE LESIONS.

Year.	Pathologically active lesions, Number and per cent of total infected.			
	Determined on enrollment.		Determined subsequent to enrollment.	
	No.	%	No.	%
1933 . . .	4	0.8	9	1.7
1934 . . .	6	0.8	6	0.8
1935 . . .	6	0.6	9	0.9
1936 . . .	6	0.5	15	1.4
1937 . . .	7	0.8	3	0.3
Total . . .	29	0.69	42	0.99

The necessity of repeated examination of all the infected by fluoroscopy, films and laboratory means is indicated in Table 5. A larger number of active cases have, as previously stated, been found subsequent to rather than at the time of enrollment. There are two

reasons. The status of minimal and sub-minimal infiltrations frequently cannot be determined by one examination, and repeated study by films and laboratory methods are necessary before proof is established that the pathologic process is active and necessitates treatment. Second, infiltrations develop among the infected whose lungs appeared normal when first examined. It would appear, therefore, that a tuberculosis program to accomplish its purpose of finding the early process must not be content with one examination done at the time of enrollment, for this offers little assurance that the group will subsequently be free of disease.

Status of Lesions Found. During the 5-year period a total of 71 or a yearly average of 14.1 active cases of pulmonary tuberculosis was found. This compares to an average number of 4 in the 14-year period from 1919 to 1933, an increase of 340%. If students enrolling prior to 1933 and subsequently discovered with tuberculosis were included, the percentage increase of cases found would be well over 400%.^{6a} This higher percentage of active cases can be largely explained by methods used in determining the status of the lesions found by roentgenologic examination. Because a very large percentage of the cases, especially those developing while the patient is in college, are in the minimal stage there is no clinical picture of tuberculosis. The individual with minimal or sub-minimal tuberculosis usually has no elevation of temperature, increase of pulse rate, physical signs or symptoms, though by laboratory examination there can be no doubt that the lesion is pathologically active. This determination of the status of the lesion is frequently possible before the roentgenogram shows any change either by retrogression or extension. Obviously, there is serious objection in waiting for the Roentgen ray film to show change before deciding whether the patient needs treatment. Progression as shown by the Roentgen ray film indicates further lung destruction with its longer period of treatment and less favorable prognosis. Fortunately, however, certain laboratory procedures are of special value in determining the status of early lesions. Repeated examination of the morning fasting gastric contents for tubercle bacilli by the staining of the centrifuged specimen and guinea pig inoculation usually indicates whether a lesion is active; aspirations are done on 3 successive mornings. The results obtained in 70 cases are presented in Table 6. Of interest is the group of 50 minimal cases in which the sputum (usually saliva) presented for examination was negative in every instance. Examination by stain of the centrifuged gastric contents showed 18% to be positive, while 72% of the minimal cases and 80% of the entire group were positive by guinea pig inoculation. The circumstance of 3 cases of pleurisy with effusion* in which tubercle bacilli were found in the gastric contents was not antici-

* The gastric contents in the fourth case of pleural effusion studied has recently been found positive

pated. In each instance the pleural fluid itself on diagnostic tap and guinea pig inoculation was negative, but in each case one or more of 3 guinea pigs inoculated with the gastric contents obtained on 3 successive mornings were positive. The presence of free tubercle bacilli in the lungs of cases of pleurisy with effusion is consistent with the frequent subsequent development of Roentgen ray visible pulmonary tuberculosis. Further study of the gastric contents in cases of pleurisy with effusion is obviously indicated.

TABLE 6.—EXAMINATION FOR TUBERCLE BACILLI.
(Sputum vs. Gastric Contents.)

Lesion.		Gastric contents.					
		Sputum +.		Stain +.		Pig +.	
		No.	%.	No.	%.	No.	%.
Minimal	50	0	0	9	18.0	36	72.0
Mod. advanced	14	4	28.5	6	42.8	14	100.0
Far advanced	1	0	0	0	0	1	100.0
Miliary	1	0	0	0	0	1	100.0
Pleural effusion	3	0	0	0	0	3	100.0
Hilum tuberculosis	1	0	0	0	0	1	100.0
Total	70	4	5.7	15	21.4	56	80.0

The presence of tubercle bacilli in the gastric contents not only proves the diagnosis, but indicates that the lesion has not healed. In 3 instances lesions 1 to 2 cm. in size have revealed the presence of tubercle bacilli by guinea pig inoculation. The procedure is furthermore a good guide in determining when treatment may safely be terminated. Commonly, especially in early cases, because there have been no symptoms or fever, and because of apparent splendid clinical progress, the patient is given unwarranted permission to return to his former activities. On 4 occasions students have returned to school with permission from sanatorium physicians, because of very apparent improvement. Study of the gastric contents, however, revealed the presence of tubercle bacilli, and in each instance subsequent extension of the process occurred. Strict adherence to the principle that tuberculous lesions of the lung should not be considered healed until tubercle bacilli are repeatedly absent in the gastric contents, would result in fewer recurrences in the many patients with apparent but not real cures.

Repeated observation of the total and differential white blood cell count has been done in a number of minimal cases for a period of months. A report of the results is not possible in this review. From observations to date, it appears that when the lymphocyte count approaches or is consistently above 30% the prognosis is favorable and the process will be found to be healing.

The erythrocyte sedimentation rate in minimal cases is frequently normal and, therefore, of little value in determining pathologic activity in the early lesion. However, an increase in the rate

usually indicates a progression of the process and this usually precedes the development of symptoms.

The Active Cases. Space does not permit presentation of a complete statistical compilation of the 71 active cases found during the 5-year period. A summary is, therefore, being given. The average age of the 23 women was 23.2 years, that of 48 men was 21.6 years, making an average age of 22.1 years for the 71 cases; 27 of these, (38%), were aware of the probable source of infection. In 4 students, evidence of a tuberculous infiltration was discernible by roentgenogram within 9 months after the Mantoux test became positive.

The site of occurrence in 40 cases was unilateral, of which 22 were in the right and 18 in the left lung. Of the 5 cases of pleural effusion 3 occurred at the right base and 2 at the left. Twenty-six of the lesions were bilateral.

Of special interest is the fact that though approximately 25% of the infected (Table 3) showed calcified lesions in the lungs or hilum glands, only 16% of the active parenchymal lesions occurred in those showing calcification. The expected number of parenchymal lesions among those showing calcified deposits was 18. The actual number was 12. Further observation may indicate that the presence of calcified lesions may be interpreted as evidence of resistance against subsequent infection.

The gastric contents were examined for tubercle bacilli in 48 individuals in this group. In 43 (89.6%) the result was positive. The expectoration submitted for examination was positive in only 10 of 69 individuals, or 14.5% of the cases.

The erythrocyte sedimentation rate was increased in 33 (47.8%) of the 69 active cases receiving the test. In the early stages of the tuberculous process the test is a less accurate indicator of the status of the lesion than are examinations of the gastric contents and the repeated studies of the differential blood.

The Mantoux test was negative, as previously indicated, in 16 (22.5%), to the smaller dose of tuberculin. The necessity for the 2-dose method or less desirable single strong dose method is obvious, if all the active cases of tuberculosis are to be found.

Pleurisy with effusion was present or had occurred in 10 (14%) of the 71 cases. Students with active tuberculosis from out of state or foreign countries numbered 15 (21%). Approximately 19% of 16,109 students studied were from states other than Wisconsin.

Mention should be made of 2 cases in the series.

CASE 1.—A male student, aged 22, had miliary tuberculosis involving the lungs, kidneys, prostate, epididymi and testicles, and on no occasion had constitutional symptoms. After surgical removal of the epididymi and one testicle, the patient spent 18 months in a sanatorium and is now again attending the University. By clinical and laboratory study he is free of all evidence of active tuberculosis.

CASE 2.—A male student, aged 19, developed pleurisy with effusion in April, 1937. No tubercle bacilli were found in his pleural fluid, but his

gastric contents were positive. After 3 months of bed rest followed by 3 months in which he gradually increased his activity, he returned to college in the fall of 1937. His weight had increased by 20 pounds since April. According to every external physical standard he was healthy. Roentgen ray, however, now showed enlargement of the hilum glands, and gastric aspirations were found positive by guinea pig inoculation. Gastric aspirations were repeated in December, 1937, and April, 1938, and were again positive. No parenchymal lesion is visible on the Roentgen ray films. The enlargement of the hilum lymph glands persists. In this case, the total white count taken at weekly intervals has been normal, and the lymphocyte has been consistently over 30%. The blood sedimentation rate was not increased. This case suggests that though some individuals may show no Roentgen ray evidence of parenchymal tuberculosis, they may have active tuberculosis and may be definitely infectious to others.

To date a favorable course has been the rule in the large majority receiving treatment. A yearly questionnaire is sent to each student having active tuberculosis. Up to the present time no one in the group has succumbed to his disease.

The stage at which the disease was discovered is presented in Table 7. The percentage of minimal cases found at the time of enrollment (41.4%) compares favorably with the 13% for the country as a whole. Highly encouraging is the number of minimal cases (73.8%) found by examinations subsequent to enrollment. Excluding the cases of pleurisy with effusion the number found in the minimal stage approaches 84%. Unfortunately, methods making possible early discovery in a very high percentage of cases are limited to a relatively small number of the total population.

TABLE 7.—STAGE OF DISEASE (ACTIVE CASES).

	Discovered on enrollment.		Discovered subsequent to enrollment.	
	No.	%.	No.	%.
Minimal	12	41.4	31	73.8
Moderately advanced	13	44.9	5	11.9
Far advanced	4	13.7	0	
Miliary	0	..	1	2.4
Pleurisy with effusion	0	..	5	11.9
Total	29	100.0	42	100.0

Summary. 1. The results of a 5-year tuberculosis program among students of a mid-western university are reviewed. The importance of discovery of early pathologic processes before symptoms have occurred is emphasized.

2. A higher rate of tuberculous infection was found among the men (29.5%) than women (24.1%). Though the rate of infection was lower in the women, the incidence of active disease among the infected was higher in the female. Study of 2944 infected men for a period of from 1 to 5 years showed that 1.63% had active pulmonary tuberculosis. Study of 1272 infected females gave an incidence of 1.8%.

3. The necessity of using tuberculin for testing to a strength of

0.005 mg. P. P. D. is indicated by the fact that 16 cases or 22.5% of cases of active tuberculosis, failed to react or gave an equivocal reaction to 0.00002 mg. P. P. D.

4. A geographic variation in the incidence of infection was found. The incidence was lowest in the North Central (25.7% of students from that region) and Mountain States (26.3%). It was highest in the Desert States (84.6%), foreign countries (67.6%), Eastern States (42.8%) and Southern States (42.4%).

5. Study of infection rates by Wisconsin counties suggests a possible correlation between the death rate and incidence of infection. Of the 14 counties having the highest tuberculosis death rate, 10 are in the most northern part of the state. No other combination of 10 counties in the state gives such a high infection rate as among students from these counties.

6. Tuberculosis is classified by describing the lesions found. The contention is held that without knowledge of when infection occurred, it becomes impossible to tell by the appearance of a lesion whether it resulted from a first infection or reinfection.

7. The tuberculous lesion resulting from the first infection is not always benign. Progressive tuberculosis has developed from known first infection.

8. The determination of the status of minimal lesions found by Roentgen ray can usually be determined by laboratory methods. The gastric contents were found positive for tubercle bacilli in 72% of 50 minimal cases by stain and guinea pig inoculation. Repeated study of the total and differential blood count may indicate the probable course of the disease before changes are noted by roentgenogram. The erythrocyte sedimentation rate usually shows an increase before symptoms develop.

9. By repeated examination of the infected at regular intervals by film and fluoroscopy, 84% of the active cases of tuberculosis (excluding pleural effusions) developing subsequent to enrollment were found in the minimal stage. Only 3 students have reported to the student clinic in the past 5 years because of symptoms (excluding pleural effusions) resulting from pulmonary tuberculosis.

10. Pleurisy with effusion was present or had occurred in 14% of the active cases.

11. Treatment of minimal tuberculosis usually results in complete healing of the lesion.

Conclusion. At present, most of society's effort in combating tuberculosis is expended in caring for patients with far advanced lesions, and death or severe physical handicap is the end result. Little of the effort is directed toward the more profitable project of determining early pathologic processes before symptoms are evident and when treatment gives a complete cure.

Until all the infected as determined by the Mantoux tuberculin test receive Roentgen ray examination at regular intervals, diag-

nosis late in the disease will continue to be the rule. Methods are available to find and establish the status of the early developing lesion. In the proper direction of our efforts lies the solution of the tuberculosis problem.

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STUDIES IN DIABETES MELLITUS.

VII. NON-DIABETIC GLYCOSURIA.*

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THE study here reported is concerned with 2,065 patients who, in the 35 years between 1900 and 1935, consulted Dr. Elliott P. Joslin and associates because of glycosuria which at the time of the original observation was thought not to be diabetic. These 2,065 patients comprise 14.8% of a total of 14,000 patients who came, during this same period†, for diagnosis or treatment of supposed diabetes. They were, in large part, referred by their family physicians because of glycosuria of significant degree found at multiple, rather than single examinations. Although symptoms suggesting diabetes were often absent, other abnormal conditions were not infrequently present. This was true particularly of hospital cases seen in consultation.

The aim of this study has been to determine how many of these patients subsequently became diabetic and to identify the factors which seemed to favor the development of the disease. In the

* Presented in preliminary form at the annual meeting of the Medical Section of the American Life Convention at Colorado Springs, June 17, 1937.

† Case 1 was seen in 1897 by Dr. E. P. Joslin. The first case of non-diabetic glycosuria, so listed, came in 1900.

course of the analysis, several other matters have been considered: for example, the mortality and causes of death of these cases. The patients were traced to May 1, 1937, or later, and their status as of the time of tracing has been used. Facts were sought regarding the present conditions of the patients, including results of recent tests for sugar in the blood and urine. In deceased patients, the recorded cause of death was ascertained and every effort was made to determine as carefully as possible whether the patient was considered to have had true diabetes, and if so, the basis for the diagnosis. By letter, telephone, telegraph or personal contact, *all but* 32 (1.5%) of the 2,065 patients were traced.

Diagnostic Methods and Standards. In this clinic the standards used for diagnosis have been reasonably uniform, particularly beginning with 1920, at which time the routine examination of the blood for its sugar content came into general use. In the summer of 1926 the records of all cases of diabetes or supposed diabetes, seen up to that time, constituting approximately 5,400 of the 14,000, were carefully scrutinized and recorded diagnoses reconsidered. In cases lacking a definite diagnosis, this was supplied after a study of data obtained from the patients' records and from information received in that year as the result of a tracing during which contact was made in one way or another with almost every patient or his family physician. It is only fair to admit that in making the classifications in 1926 it was possible to use hindsight in addition to foresight and consequently a few cases then were reclassified as diabetic as of first visit. The results on these earlier cases have been to some extent biased thereby.

Four major diagnoses have been made according to the standards listed below.

The diagnosis of *diabetes mellitus* has been made when a patient with glycosuria has been found to have a fasting blood sugar (venous) of 0.14% or above or a postprandial blood sugar of 0.17% or above. These standards may with justification be criticized on two grounds: It is possible that the value of 0.14 is too high and that one of 0.13% is high enough to be considered diagnostic. Furthermore, and we think with more justification, in some cases, particularly those in which the diagnosis is made on the basis of a glucose tolerance curve, the postcibal value of 0.17% may be regarded by some as too low. However, over a period of years these standards have worked very well and we have continued to use them for the sake of uniformity. When using capillary blood, we have required that the postprandial blood sugar be 0.20% or above in order to make the diagnosis of diabetes and experience suggests that even this is not allowing enough difference between venous and capillary values. Thus in one case (13368) at two different intervals of time following the giving of glucose, the capillary-venous difference amounted to 0.08%.

Folin's²⁻⁴ methods of analysis have been used throughout.

The diagnosis of *potential diabetes* is not often made and its criteria are not rigid or well-defined. We have at times discussed discontinuing such a classification but upon each occasion valid reasons persuaded us to retain it. In general, it has represented a clinical impression and has been reserved for those cases with a fasting blood sugar of 0.12 or 0.13%, a postprandial value of 0.15 or 0.16% and glycosuria dependent upon diet, particularly if the patient has a history of diabetes in the family.

Renal glycosuria in the limited sense in which we have used it denotes constant glycosuria even in the fasting state, fasting blood sugar values below 0.12%, postprandial values below 0.17% and an absence of diabetic symptomatology. The typical sugar tolerance curve is, however, almost flat, with a normal initial value. Patients with renal glycosuria in this series are, therefore, individuals whose renal threshold for sugar is extremely low, usually corresponding to a blood sugar of 0.10% or lower. In previous articles on renal glycosuria^{6a,b} considerable emphasis has been placed upon a time element essential for the diagnosis and an arbitrarily chosen period of 3 years has been established as necessary. However, excluding cases of temporarily marked lowering of the renal threshold as seen notably in pregnancy, the necessity of such a time interval is doubtful. If one finds glycosuria constantly even in the fasting state in a patient without diabetic symptomatology and if during a glucose tolerance test an unequivocally normal response is obtained, the chances are overwhelming that one is dealing with renal glycosuria. Caution must be advised against accepting as normal, tolerance curves which either at the highest point or subsequent fall are on the borderline of the type found in mild diabetes. Patients showing such curves should be kept under close observation and reexamined at suitable intervals before making a definite diagnosis.

It is evident from the above that many transient or intermittent glycosurias often referred to as "renal glycosuria" are excluded from such a classification in this paper.

Although the cases of glycosuria of pregnancy usually represent instances of a lowering of the renal threshold for sugar, the condition is transient, lasting only for the duration of the pregnancy. This characteristic sets this group sharply apart from that in which there is a permanently lowered renal threshold.

The "*unclassified*" glycosuria group is the residual class into which all other cases of glycosuria are placed. This group includes cases of alimentary glycosuria, those with a renal threshold for sugar slightly below the average, also patients with infections or toxemias, with chronic or degenerative conditions, with hyperthyroidism and hyperpituitarism, and with various other conditions, which may at times cause glycosuria which is usually temporary and slight. In many of these patients, despite the history of glycosuria, no urinary sugar was found during the period of initial observation.

Under the heading of "*deferred diagnosis*" have been placed those patients, most of them recently seen, for whom, up to the time of the present study, available data were inadequate for proper diagnosis.

In establishing the diagnosis in any individual case the following procedure has been employed: Random urine and blood specimens are obtained at the patient's first visit regardless of the time of day. If the values for the blood sugar are below those accepted as indicating diabetes, the patient may be requested to return for similar tests at 45 to 60 minutes after an ordinary mixed meal liberal in carbohydrate. In an attempt to establish the diagnosis at the initial visit, particularly in patients who may not be seen again, 50 gm. of glucose may be given orally at this time and blood and urine tests made 45 to 60 minutes later.

If these convenient diagnostic steps do not enable one to make a diagnosis, then recourse is had to a formal sugar tolerance test. At present and for the most part, we have used 100 gm. of glucose as the test load for adult patients, although for a few years prior to January 1, 1935, at Professor Folin's suggestion, we used 75 gm. of sucrose. Starting with the patient in the fasting state or 5 hours after a meal, samples of urine and venous blood are taken before the giving of sugar and at $\frac{1}{2}$, 1, 2 and occasionally 3 hours afterward. Interpretation is based both upon the height and the subsequent rate of fall of the curve obtained.

The authors and their associates freely concede the difficulties which are occasionally encountered by close adherence to rigid diagnostic standards such as those outlined above. The chief error, if such there be, arises in the classification of a glycosuric patient as a diabetic simply because a venous blood sugar value of 0.17% is obtained. However, one must have definite standards of diagnosis and abide by them, since otherwise confusion is inevitable. One cannot rely on clinical symptoms because of the well-known absence of such in certain stages of the disease in patients with undoubted diabetes. Fortunately, those situations in which diagnosis is difficult are not common enough to change the outcome of this analysis. Parenthetically, it should be stated that in the actual treatment of the patient, conclusions from laboratory data are modified by clinical judgment.

Description of Material. The 2,065 patients mentioned at the beginning of the paper include (a) 38 patients who, after further study within 3 months of the time of the initial visit, were diagnosed as diabetic ("*reconsidered*" diagnosis), or on whom subsequent review of the data of original examination showed an error in the diagnosis and who, therefore, were diabetic from the start ("*rejected*" change of diagnosis); (b) 81 patients classed as "*deferred*" on whom the data did not permit a definite diagnosis. If these 119 cases are excluded, the number of non-diabetics was 1,946, or 13.9% of the original group of 14,000 patients.

These 1,946 cases which exclude the *rejected*, *reconsidered* and *deferred* diagnoses, form the actual basis of the present study. Of this total, 1,142 were males and 804 females, divided according to age as shown in Table 1.

With regard to the date of initial observation, 197 came first to the clinic prior to 1920, 1,097 in the decade 1920 to 1929, and 652 between 1930 and October, 1935.

TABLE 1.—SEX AND AGE DISTRIBUTION OF PATIENTS WITH NON-DIABETIC GLYCOSURIA. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, BOSTON, MASS., 1900-1937.

Age at first visit.	Total.	Males.	Females.
All ages	1946	1142	804
Under 20	363	215	148
20 to 39	648	337	311
40 to 59	688	443	245
60 and over	247	147	100
Average age	37.7 years		

Medical examination for life insurance was the basis of the history of glycosuria in 285, or 14.6% of the group. The proportion of such cases varies widely by sex and age, in accordance with the typical make-up of the group of persons applying for insurance requiring such examination. Thus, 23.1% of the males and only 2.6% of the females were referred because of glycosuria discovered at examination for insurance. The percentages were nominal among males under 20 and over 60, but between those ages, over 30% came because of the findings at an insurance examination.

Incidence of Various Types of Non-diabetic Glycosuria. Table 2 shows the number and percentage of cases in each classification. The original diagnoses are given for all 2,065 patients, including the 38 *rejected* or *reconsidered* and the 81 *deferred* diagnoses, and the final diagnoses for the 1,946 considered to fall within the scope of this paper. The authors have felt that these excluded cases should be mentioned, but should not enter into the subsequent analysis.

Potential diabetes was the diagnosis in 12.0% of the total cases, and 12.3% of the definitely non-diabetic group. *Renal glycosuria* accounted for 3.2% of the original diagnoses, but only 2.3% of the final non-diabetic classification. *Deferred* diagnoses accounted for 3.9% of the total. By far the largest group, containing more than 80% of the cases, consisted of those with *unclassified glycosuria*.

Changes of Diagnoses Within the Non-diabetic Classification. These internal changes are relatively few but have special significance. The originally rather loose concept of renal glycosuria has been modified in this clinic in late years to include only those cases with an extremely low renal threshold for sugar; such rigid requirements have reduced the number of cases. In the judgment of the associ-

ates of the George F. Baker Clinic, no patient with true renal glycosuria has progressed to diabetes. The records of the 3 patients

TABLE 2.—ORIGINAL AND FINAL CLASSIFICATIONS OF PATIENTS WITH NON-DIABETIC GLYCOSURIA. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Classification.	Original classification.		Final classification excluding reconsidered, rejected and deferred diagnoses.*	
	Number.	Per cent.	Number.	Per cent.
Total	2065	100.0	1946	100.0
Potential diabetes	247	12.0	240	12.3
Renal glycosuria	67	3.2	45	2.3
Glycosuria of pregnancy	8	0.4	9	0.5
Pentosuria	3	0.1	3	0.2
Levulosuria	1	..	1	0.1
Diabetes mellitus	1
Diabetes insipidus	1	..	1	0.1
Unclassified	1656	80.2	1647	84.6
Deferred	81†	3.9

* The changes in the excluded cases are as follows:

Of 25 rejected changes (cases now considered diabetic from the beginning), 8 were originally diagnosed as potential diabetics, 2 as renal glycosurics and 15 as unclassified.

Of 13 reconsidered (cases for whom additional data within 3 months proved the patients diabetic), 3 were originally diagnosed as potential diabetics and 10 as unclassified.

† Includes 1 case definitely proved pentosuric early in 1938.

in whom the diagnosis of renal glycosuria was made originally and at a later date changed to diabetes, have been carefully studied. In each case the original diagnosis of renal glycosuria has been discarded as unwarranted by the data available. Even more cases originally classified as renal glycosuria have been rediagnosed as unclassified glycosuria because they did not conform to the diagnostic criteria previously stated. Subsequent review of the original records at various times or subsequent observations of patients have caused changes in the diagnosis of a few other cases from one non-diabetic classification to another. The total number of changes within the non-diabetic classification was 34. The frequency of each type of change is shown in the following table.

CHANGES FROM ONE NON-DIABETIC CLASSIFICATION TO ANOTHER.

From.	To.	Number of cases.
Renal glycosuria	Potential diabetes	1
Renal glycosuria	Unclassified	23
Potential diabetes	Renal glycosuria	1
Potential diabetes	Glycosuria of pregnancy	1
Unclassified glycosuria	Renal glycosuria	2
Unclassified glycosuria	Potential diabetes	5
Diabetes mellitus	Renal glycosuria	1

Subsequent Incidence of Diabetes. Of the 1,946 patients forming the basis of this study, in 193 (9.9%) subsequent findings up to the

date of tracing in 1937 have warranted the assumption that true diabetes mellitus has developed. The subsequent incidence of diabetes according to the final non-diabetic classifications was 40 (16.7%) of the *potential* diabetics; one (11.1%) of the patients with *glycosuria of pregnancy*; and 152 (9.2%) of the *unclassified* cases. As already stated, no case of renal glycosuria (in the limited sense used in this Clinic) has developed diabetes. This fact is emphasized to bring out the lack of relationship between the two conditions. In our opinion, renal glycosuria is not a true disease but simply a striking deviation from the average normal as regards the renal threshold for sugar. Patients with diabetes may also have renal glycosuria. It seems reasonable that if one could follow for a period of years a sufficiently large group of individuals with a very low renal threshold for sugar, some of them, possessing certain favoring influences such as obesity and the presence of diabetes in relatives, would develop diabetes mellitus just as do persons in the general population with an average normal threshold. Such development of diabetes would not necessarily, however, signify any connection between the two conditions.

As we have previously indicated, all but a small number of the patients have been traced at least to May 1, 1937, but some were not traced until later and any diabetics discovered subsequent to May 1, 1937, have been included in the total. The following sections take up the chief factors in the onset of diabetes in these cases.

Age. As Table 3 shows, the percentage of changed diagnoses increases with advancing age in the four broad age groups distinguished. The rise is marked prior to age 60, but increases very little after that age.

TABLE 3.—AGE IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES AMONG NON-DIABETIC GLYCOSURICS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age at examination.	Subsequent diabetes.	
	Number.	Per cent.
All ages	193	9.9
Under 20	9	2.5
20-39	39	6.0
40-59	104	15.1
60 and over	41	16.6

Sex. No significant difference by sex in the subsequent incidence of diabetes was found (see Table 4). The data are given by age. They show that this negative finding according to sex is not a result of age differences between the two sexes. On the basis of this result, therefore, no subsequent distinction by sex has been made.

Weight. The percentage of cases developing diabetes increases distinctly with weight. This phase of the study has been made both from the point of view of the weight found at the initial examination and on the basis of the previous maximum weight. The patients have been classified at both dates according to the percentage departure from average weight, with allowance for sex, height and age.

TABLE 4.—SEX IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES AMONG NON-DIABETIC GLYCOSURICS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age at examination.	Subsequent diabetes.			
	Per cent.		Number.	
	Males.	Females.	Males.	Females.
All ages	10.2	9.6	116	77
Under 20	2.8	2.0	6	3
20-39	5.9	6.1	20	19
40-59	14.4	16.3	64	40
60 and over	17.7	15.0	26	15

Weight at Initial Examination. At all ages only 6.0% of those underweight at examination developed diabetes, as compared with 10.6% of those of average weight, 12.0% of those less than 20% overweight and 16.6% of those 20% or more overweight. This trend is consistent in all age groups in which there are sufficient numbers of cases to give reliable ratios.

Previous Maximum Weight. The data based upon the maximum weights before initial visit give even more clear-cut differences than do those based upon weights at the first visit. The latter have been presented first because they represent actual observations and are, therefore, more strictly accurate than the maximum figures reported by the patient. For certain uses also, such as insurance work, the data as of initial examination are more practicable because reliable data on weights previous to examination are seldom available to the physicians of life insurance companies.

At all ages, the incidence of subsequent diabetes, according to previous maximum weights, rises successively from a minimum of 3.2% among underweights to a maximum of 17.0% among those 20% or more overweight. This trend is present in all age groups except the youngest, those under 20 at original observation. The data on build at examination and at previous maximum weight are given in Table 5.

Heredity. The presence or absence of a family history* of diabetes at first glance (see Table 6) would seem to have had little or no

* Within restricted degree of relationship, viz., parents, grandparents, children, siblings, uncles and aunts, and first cousins.

influence upon the subsequent incidence of the disease in these patients with non-diabetic glycosuria. Among those with a positive

TABLE 5.—BUILD IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES MELLITUS AMONG NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY PERCENTAGE DEPARTURE FROM AVERAGE WEIGHT, FOR SEX, HEIGHT AND AGE (a) AT EXAMINATION AND (b) AT MAXIMUM WEIGHT PRIOR TO EXAMINATION. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age at initial examination.	Build group.							
	Per cent becoming diabetic.				Number becoming diabetic.			
	Under-weight.	Average weight.	Overweight.		Under-weight.	Average weight.	Overweight.	
			5% to 19%.	20% and over.			5% to 19%.	20% and over.
Weight at initial examination								
All ages	6.0	10.6	12.0	16.6	38	46	46	39
Under 20	5.3	1.0	4.5	6	1	..	1
20-39	3.3	6.8	9.0	10.3	8	10	10	8
40-59	8.7	16.1	19.0	23.6	18	22	28	25
60 and over	8.1	27.1	18.6	17.2	6	13	8	5
Previous maximum weight								
All ages	3.2	4.2	11.9	17.0	7	13	55	94
Under 20	3.0	2.9	2.2	5.9	1	1	1	1
20-39	3.0	2.3	7.5	9.2	3	3	13	16
40-59	4.4	5.7	13.6	23.0	3	6	25	60
60 and over	8.1	26.7	16.7	..	3	16	17

TABLE 6.—HEREDITY IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES MELLITUS AMONG NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC AMONG GROUPS CLASSIFIED ACCORDING TO FAMILY HISTORY OF DIABETES. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age at examination.	Subsequent diabetes.			
	Per cent.		Number.	
	Positive family history.	Negative family history.	Positive family history.	Negative family history.
All ages	10.0	9.9	51	142
Under 20	4.7	0.9	7	2
20-39	7.8	5.3	14	25
40-59	16.9	14.7	24	80
60 and over	15.0	16.9	6	35

family history, the percentage at all ages combined of patients with non-diabetic glycosuria who became diabetic was 10.0%, as compared with 9.9% among those with a negative family history. The group

with a positive family history, however, is definitely younger, about 9 years on the average, than that with a negative family history, and as Table 6 shows, when the data are analyzed according to age, the percentage becoming diabetic is higher in the positive family history group than in the negative group, except at ages 60 and over. The younger the age, the greater is the difference. If the proportion of those becoming diabetic were the same at each age in the positive group as in the negative group, the number becoming diabetic in the positive heredity group would be only 39, as compared with 51 actually found. On the basis of this analysis, one may draw the conclusion tentatively that heredity is a factor in the subsequent development of diabetes in the younger patients with glycosuria.

Duration. The length of time elapsed since original observation obviously must be of importance unless all the cases of diabetes among these patients were to develop within a relatively short time after examination. This is clearly not the case. Consequently, when the incidence of diabetes is noted for groups first observed before and since 1927, much higher percentages of changed diagnoses

TABLE 7.—DURATION SINCE EXAMINATION IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES AMONG NON-DIABETIC GLYCOSURICS. COMPARISON OF PATIENTS FIRST OBSERVED PRIOR TO AND SINCE 1927. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age at examination.	Subsequent diabetes.			
	Per cent.		Number.	
	First examined prior to 1927.	First examined 1927 and later.	First examined prior to 1927.	First examined 1927 and later.
All ages	14.4	6.4	124	69
Under 20	5.6	1.2	6	3
20-39	8.0	4.2	25	14
40-59	21.0	9.3	72	32
60 and over	21.2	13.5	21	20

are found in every age group among the earlier cases than among the later ones. At all ages combined, 14.4% of the earlier group of patients have become diabetic, compared with only 6.4% of the more recent group. The actual difference is probably somewhat larger, since at least a few early cases were reclassified as diabetic at first observation, when the records were reviewed in 1926, and thus do not enter this experience. On the other hand, in the earlier group, diagnostic procedures were not as well developed or standardized as since 1927; consequently, the later cases which have been more thoroughly studied are less subject to error of diagnosis. The proportions becoming diabetic in the groups first observed before and since 1927 are given in Table 7.

In the divisions of the material presented thus far, duration has not biased the results, but in the subsequent section relating to diagnostic procedures which have changed during the period covered in this study (*e. g.*, blood sugar examinations and tolerance tests), the matter is vital. In such cases the proportions of changed diagnoses *in relation to the years of life exposed* give a more accurate picture when there are differences in average duration between the groups compared. This is brought out by Table 8 which gives the proportions becoming diabetic per 1,000 years of life exposed for the same groups used in Table 7, namely, patients first coming under observation prior to 1927 and those since 1927. On this basis, the ratios, for the early and the more recent patients, are almost identical. At no point is there a really significant difference. To a certain extent, this is surprising, because the average attained age of the earlier cases is greater and one would on that account alone expect a higher proportion of subsequent diabetes among them than among the more recent cases. This result, however, probably reflects the fact that the original classification of some of these cases was made shortly before 1927 and there probably is some bias in the earlier material on that score. Reference to this matter has been made earlier.

TABLE 8.—SUBSEQUENT INCIDENCE OF DIABETES PER 1000 YEARS OF LIFE EXPOSED AMONG PATIENTS WITH NON-DIABETIC GLYCOSURIA FIRST EXAMINED PRIOR TO 1927 AND THOSE FIRST EXAMINED IN 1927 AND LATER YEARS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age at examination.	Subsequent diabetes per 1000 years of life.	
	First examined prior to 1927.	First examined 1927 and later.
All ages	11.8	11.3
Under 20	4.1	2.1
20-39	5.7	7.0
40-59	18.3	16.3
60 and over	27.5	30.1

Age, Maximum Weight, Family History and Duration Considered Simultaneously. The foregoing analysis, which has shown age and weight and duration as distinct factors favoring incidence of diabetes in non-diabetic glycosuria, heredity as a slight influence and sex as of no influence, assumed for each item that the data were unbiased as to other items, except with regard to age which has been consistently taken into account. In order to test the validity of this assumption and, therefore, of the differences found, the data have been split into smaller groups in which all these factors are taken into account. To avoid having to deal with groups that are too small to give reliable results, however, average and underweights are combined and overweights are considered as a class.

The results of this division of the material (Table 9) confirm the individual items which were found of positive influence, and bring out their relative importance. Build and age are of approximately equal influence. The former is possibly of slightly greater importance, because in very few instances is there a higher percentage of subsequent diabetes in the lighter weight group than in overweights,

TABLE 9.—INFLUENCE OF SEVERAL FACTORS CONSIDERED SIMULTANEOUSLY ON SUBSEQUENT INCIDENCE OF DIABETES MELLITUS AMONG NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY AGE AT EXAMINATION, PREVIOUS MAXIMUM WEIGHT AND PRESENCE OR ABSENCE OF DIABETES IN THE FAMILY. PATIENTS FIRST SEEN PRIOR TO AND SINCE 1927 SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Heredity; age at examination.	Per cent becoming diabetic.				Number becoming diabetic.			
	First examined prior to 1927.		Examined 1927 or later.		First examined prior to 1927.		Examined 1927 or later.	
	Average or under-weight.	Over-weight (5% or more).	Average or under-weight.	Over-weight (5% or more).	Average or under-weight.	Over-weight (5% or more).	Average or under-weight.	Over-weight (5% or more).
Total								
All ages . . .	4.9	21.0	3.0	9.2	11	99	9	50
Under 20 . .	4.3	10.0	2.2	1	2	1	..
20-39 . . .	1.9	11.8	3.1	5.1	2	20	4	9
40-59 . . .	7.7	26.7	3.2	11.4	6	60	3	25
60 and over	11.1	29.3	2.9	15.4	2	17	1	16
Positive family history of diabetes mellitus								
All ages . . .	4.7	21.0	4.3	7.5	2	26	4	10
Under 20 . .	9.1	22.2	4.0	1	2	1	..
20-39 . . .	5.3	9.6	5.1	6.1	1	5	2	3
40-59	35.2	6.7	..	19	..	3
60 and over	14.3	23.5	1	4
Negative family history of diabetes mellitus								
All ages . . .	5.0	21.0	2.4	9.7	9	73	5	40
Under 20
20-39 . . .	1.2	12.8	2.3	4.7	1	15	2	6
40-59 . . .	8.8	24.0	4.1	12.6	6	41	3	22
60 and over	13.3	34.7	13.8	2	17	..	12

whereas in a few groups of average weight or less, the increase by age is not marked or is absent. This confirms the previous observation that build is a vital factor except at ages under 20. Rather large differences were fairly consistently found by duration, but these were inevitable and were less marked than might be expected, especially when the greater attained age of the earlier cases is taken into account. The slight influence of heredity is again brought out, for there was no consistent difference between the heredity and

non-heredity groups when the other factors were simultaneously considered.

Jewish and Non-Jewish Patients Compared. The subsequent incidence of diabetes was much greater among Jewish patients originally diagnosed as non-diabetic than among non-Jewish patients. This observation holds at every age, even though the numbers in certain of the groups are rather small. In this analysis, the factor of sex has been considered and it was found that the subsequent incidence of diabetes was particularly high in females. The facts are given in Table 10.

TABLE 10.—SUBSEQUENT INCIDENCE OF DIABETES IN JEWISH AND NON-JEWISH PATIENTS WITH NON-DIABETIC GLYCOSURIA. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age at examination.	Subsequent diabetes.											
	Per cent.						Number of cases.					
	Both sexes.		Males.		Females.		Both sexes.		Males.		Females.	
	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.
All ages . . .	18.5	7.9	16.8	8.6	20.9	6.9	68	125	36	80	32	45
Under 20 . . .	5.4	2.0	6.5	2.2	4.0	1.6	3	6	2	4	1	2
20-39 . . .	14.3	3.6	13.9	3.5	14.7	3.7	21	18	11	9	10	9
40-59 . . .	25.7	12.4	21.1	12.7	34.0	11.8	36	68	19	45	17	23
60 and over . .	33.3	14.8	28.6	16.5	40.0	12.2	8	33	4	22	4	11

Analysis of the records of Jewish patients shows that the proportion of overweights was higher than among non-Jewish patients, but even when allowance was made for that and also for duration since first observation, the incidence of diabetes was still significantly higher among the Jewish patients than among non-Jews.

Adequate Study. The care with which the patient is studied should be considered in relation to the subsequent incidence of diabetes. A group of patients termed by us the "adequate study" group has been distinguished, in which have been included those with two or more blood sugar values (at least one of them at 20 to 60 minutes after a meal) at original observation.*

Table 11 shows the subsequent incidence among the group with "adequate study" as compared with other patients. In this table the proportions becoming diabetic are presented not only as percentages but also as rates of changed diagnosis per 1,000 years of life exposed. The latter basis is the more accurate, because the procedures for more thorough study of patients have been gradually

* This period covers the first 3 months after initial observation.

introduced and therefore most of the "adequately studied" patients have been seen in comparatively recent years. The experience on patients first observed prior to and since 1927 has also been distinguished. The comparisons between the more recent patients have greater validity.

TABLE 11.—ADEQUACY OF ORIGINAL STUDY IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES IN NON-DIABETIC GLYCOSURICS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Age groups; examination years.	Subsequent diabetes.											
	Per 1000 yrs. of life exposed.				Per cent				Number of cases.			
	Adequately studied*				Adequately studied*				Adequately studied*			
	Total.	Without tolerance test.	With tolerance test.†	Others.	Total.	Without tolerance test.	With tolerance test.†	Others.	Total.	Without tolerance test.	With tolerance test.†	Others.
Total.												
All ages	10.3	11.7	6.3	12.6	7.4	10.2	3.1	12.5	74	62	12	119
Under 20	3.1	4.7	3.0	2.1	4.0	2.9	4	4	..	5
20-39	7.3	8.2	4.8	5.1	5.8	8.1	2.6	6.3	22	18	4	17
40-59	15.9	18.5	7.2	18.8	11.6	15.6	3.7	18.3	38	34	4	66
60 and over . . .	18.8	14.3	36.0	34.6	9.8	8.5	12.9	21.4	10	6	4	31
Examined 1927 and later												
All ages	10.4	12.8	7.2	13.0	5.7	8.4	3.3	7.5	41	29	12	28
Under 20	1.1	1.9	3.5	0.6	1.4	2.0	1	1	..	2
20-39	7.0	8.6	5.5	6.8	4.0	6.1	2.7	4.5	10	6	4	4
40-59	16.6	21.4	8.5	15.6	9.3	13.9	3.9	9.2	21	17	4	11
60 and over . . .	24.7	19.7	36.0	36.8	10.6	9.3	12.9	17.5	9	5	4	11
Examined prior to 1927												
All ages	10.1	10.9	12.5	11.8	12.5	15.7	33	33	..	91
Under 20	7.7	9.4	2.8	9.7	11.1	3.9	3	3	..	3
20-39	7.5	8.0	4.7	9.2	9.8	7.1	12	12	..	13
40-59	15.1	16.3	19.6	16.7	17.7	22.8	17	17	..	55
60 and over . . .	6.0	6.0	33.4	5.9	5.9	24.4	1	1	..	20

* At least 2 blood sugar values, one of them at 20 to 60 minutes after a meal.

† Cases with tolerance test within 3 months of first visit.

The most striking difference in the table is the markedly lower proportion of subsequent diabetes in those given a glucose tolerance test at first observation. This result probably reflects the successful diagnosis at original observation of mild diabetes in many patients who therefore are excluded from the non-diabetic series. Apart from this group, the differences between the "adequately studied" cases and the rest are slight and inconsistent. Most certainly the relatively high incidence of subsequent diabetes among the "adequately studied" cases reflects the large number of cases of difficult diagnosis in the group and not faults in the routine of study. In judging the results of the comparison of the more carefully studied cases with the others, this consideration must be kept in mind.

It must be acknowledged that the percentage becoming diabetic among those given a tolerance test, low as it is, is higher than expected. In 4 of the 12 patients in this group, the original tolerance

test was faulty in that it was carried out at 1 hour after breakfast and for this reason the results cannot be accepted as entirely valid. Experience has shown that a fast of at least 5 and preferably 12 hours is advisable before giving the sugar used as a test load. In 7 of the 12 cases sucrose was given; our experience suggests that more uniform results are obtained with glucose. In 4 of the 12 cases the original tolerance curves were difficult to interpret and were not strictly normal because, despite the fact that no blood sugar value higher than 0.16% was obtained during the tests, the 2-hour values were not absolutely normal. Case 8131, a physician and the only fatal case in the group, died at the age of 74.2 years with renal block and uremia. He had never considered that he had diabetes. Terminally he developed glycosuria and marked hyperglycemia. Case 8809 was 3 months pregnant in August, 1933, when the second tolerance test at which diabetes was diagnosed was carried out; in May, 1937, she considered herself well and was taking no insulin. Only 3 of the 12 cases have developed diabetes of a degree that insulin was or is needed and in 2 of these the original tolerance curve was not strictly normal. In 2 other cases, abnormal blood sugar values had been obtained elsewhere prior to the first visit here.

It is clear that in the majority of these 12 cases unusual circumstances existed. In 4 cases, however, there seems to have been definite progression from an unimportant to a significant impairment of carbohydrate tolerance.

Blood Sugar Level at Original Examination. The subsequent incidence of diabetes among patients thought to have non-diabetic glycosuria at first visit increases with the level of the blood sugar at the initial observation. The rate is low among those with low or normal blood sugars and is high (30.5%) among those with a blood sugar level close to that of true diabetes (0.13%). Table 12 gives the results of an analysis according to blood sugar at first examination. Three groups of blood sugar values are distinguished, namely, fasting, at 1, and at 2 or more hours after food or sugar (glucose or sucrose). There were too few observations at other intervals to permit study. Cases have been used once at each of these intervals, for which a reading appears in the record. Where two or more observations for a particular interval (*e. g.*, in the fasting state) were available for a given patient, the highest was used. The data in this table indicate the importance of subsequent tests particularly on those patients with suspicious or borderline blood sugar values. The percentages becoming diabetic rose as high as one-fourth to one-third or more of the cases in certain groups. The fasting and 2-hour values gave more distinct results than the 1-hour readings. This may, however, be purely an artefact. There are few borderline readings at 1 hour after food, possibly because a stricter diagnostic attitude was taken for those with a borderline

postprandial blood sugar. It is notable that age is a factor in this analysis also. The percentage of subsequent diabetes increases with age in most of these blood sugar groups.

TABLE 12.—BLOOD SUGAR LEVEL AT ORIGINAL EXAMINATION IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES IN NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY BLOOD SUGAR VALUES. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Blood sugar, per cent.	Subsequent diabetes.							
	Per cent.				Number of cases.			
	All ages.	Under 40	40-59	60 and over.	All ages.	Under 40	40-59	60 and over.
Fasting								
.08 or less . .	6.4	4.8	10.3	7	3	4	..
.09-.10 . .	8.8	6.7	10.2	13.6	15	6	6	3
.11-.12 . .	23.9	12.1	33.3	18.2	22	4	16	2
.13 or more* .	30.5	15.0	36.7	30.8	25	3	18	4
One hour p. c.								
.12 or less . .	4.1	3.3	5.5	5.9	8	4	3	1
.13-.14 . .	13.1	7.4	22.7	8.3	8	2	5	1
.15-.16 . .	12.8	18.8	33.3	5	..	3	2
Two hours or more p. c.								
.08 or less . .	4.8	3.5	6.3	8.3	7	3	3	1
.09-.10 . .	5.3	2.8	4.5	17.6	14	4	4	6
.11-.12 . .	13.5	4.1	23.2	19.2	21	3	13	5
.13 or more . .	31.7	22.2	37.8	44.4	26	8	14	4

* The figures in this line indicating the subsequent incidence of diabetes in patients with a fasting blood sugar of "0.13% or more" must not be interpreted too strictly. Naturally the reader recalls statements earlier in this paper to the effect that a fasting blood sugar of 0.14% is considered diagnostic of diabetes and hence wonders why the cases now under discussion were not so classified at original observation. The reasons were various but chiefly: (1) lack of accompanying glycosuria; (2) lack of confirmation of diagnosis by subsequent tests of blood and urine; (3) questionable values; (4) failure to record time of day blood was drawn; (5) complicating conditions in themselves capable of producing transient slight abnormalities in the blood sugar.

Striking also are the results of the analysis in cases with readings at two or more intervals, with relation to food or glucose. This analysis is restricted to the same three intervals as the preceding section, namely, fasting, 1 hour and 2 hours or more after food. While the numbers are small, the results are definite. The proportion of patients subsequently becoming diabetic is highest when both of two readings are above average and lowest when both are normal. The results were equally significant in the groups with *fasting—1 hour*, and *fasting—2 hour or more* blood sugar readings. The comparative level of the fasting and 2 hour or more blood sugars yielded negative results.

Comparison of Probability of Becoming Diabetic for Non-diabetic Glycosurics and Unselected Population Groups. The question may

properly be raised as to whether the incidence of diabetes among patients with non-diabetic glycosuria is any higher than that for a group of persons picked at random. The answer is decidedly in the affirmative, although exact measurement cannot be made of the relative incidence of diabetes in the two groups. The incidence of diabetes in random groups may be measured by the probability

TABLE 13.—BLOOD SUGAR LEVEL AT TWO INTERVALS IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES IN NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY BLOOD SUGAR LEVELS.* EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Blood sugar, per cent.	Subsequent diabetes.	
	Per cent.	Number of cases.
Fasting (A) and one hour (B)		
A = .11 or more and B = .14 or more	67	4
A = .11 or more or B = .14 or more	17	3
A = .10 or less and B = .13 or less	7	4
Fasting and two hours		
Both .11 or more	75	3
Either .11 or more	13	1
Both .10 or less	9	2
One hour (C) and two hours (D)		
C = .14 or more and D = .11 or more	25	1
C = .14 or more or D = .11 or more	13	2
C = .13 or less and D = .10 or less	5	2

* Where consecutive blood sugar values were available after a test meal or tolerance test, these were used, in preference to the highest values of the fasting, 1 hour and 2 hour or more specimens, taken on different occasions. When the data were available for the three intervals, the case was tabulated in all three combinations of the table.

of eventually dying of diabetes, computed from mortality statistics of the general population.^{5a} On the basis of 1930 statistics for the United States, the probability of eventually dying from diabetes was slightly over 2% at age 10. For males it was 1.6% and for females 2.9%. The maximum figure for males was 1.8%, recorded about age 50, and for females 3.1% also about the same age. Even if one doubles the figures to allow for deaths of diabetics ascribed to

other causes, the highest figures at any age would not exceed 3.6% for males and 6.2% for females. These are far below the percentages recorded among the non-diabetic glycosurics, even within the short period of actual observation, namely, 9.9% for the experience as a whole and 15.5% among those 40 or over at first observation. The contrast would be even greater on the basis of the *eventual* incidence of diabetes among the non-diabetic glycosurics, because such incidence figures will be much higher than those for the relatively limited period of time elapsed since first observation.

Mortality. The mortality experience up to May 1, 1937, on these patients with non-diabetic glycosuria has been tabulated according to standard insurance practice, in the same manner as for diabetic patients of the clinic, previously reported.^{5b} Separate tabulations were made for cases coming first under observation prior to 1927 and since that time. The experience on the earlier cases was divided at 1927 to permit proper comparison of the experiences on earlier and more recent cases. The mortality of these patients was compared with that prevailing among insured lives. Because the experience covers a long period during which there has been a decided decrease in mortality of insured persons over most of the life span, separate mortality tables have been used to evaluate the experience prior to 1927 and since that date. In the earlier part of the experience, we have used the American Men (Ultimate) Table based upon standard insured lives during 1901 to 1916. For the years 1927 and later, we have used the Combined Annuity Table* for males which is based upon the mortality of clerks insured under group policies during 1922 to 1926. The earlier table excludes the so-called "select" period during which a low mortality exists because of medical selection. By its very nature, the later table has no "select" period. The comparative results are given in the form of ratios of actual deaths to the number expected if these patients had had the same mortality as experienced by insured lives.

On the basis of the insurance tables, the mortality of these non-diabetic glycosurics has been generally above the average. This is brought out by Table 14, which gives the ratios of actual to expected deaths, for the several divisions of the experience already described, at all ages combined, and in three broad attained age groups—under 45, 45 to 64, and 65 and over. For reasons stated below, the table gives data also for the experience with the first year after observation excluded.

For the experience as a whole, the mortality is about one-third higher than among insured lives. Patients seen prior to 1927 have

* Unfortunately no better insurance table covering the period between 1927 and 1937 is available. The table used, however, is a rather rigid standard, because the mortality of clerks is at most ages appreciably below the average for all employed persons.

had a relatively lower mortality than those first observed since that year. Among the earlier patients, at all ages combined, the mortality ratios before and since 1927 have been about the same.

Considered by age, the results were somewhat better under 65 than over that age. This has been true, however, only for patients first seen prior to 1927. In the more recent group, the ratios are higher, though not significantly so, under age 65 than over that age.

TABLE 14.—COMPARATIVE MORTALITY OF PATIENTS WITH NON-DIABETIC GLYCO-SURIA AT ORIGINAL EXAMINATION. ACTUAL DEATHS AND RATIO TO NUMBER EXPECTED BY AMERICAN MEN (ULTIMATE) TABLE FOR EXPERIENCE PRIOR TO 1927 AND BY COMBINED ANNUITY TABLE (MALES) FOR EXPERIENCE SINCE 1927. TOTAL EXPERIENCE* AND EXPERIENCE EXCLUDING FIRST YEAR SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Examination year; attained age.	Total experience.*						Experience excluding first year.					
	Per cent actual of expected deaths.			Actual deaths.			Per cent actual of expected deaths.			Actual deaths.		
	1900- May 1, 1937.	1900-1926.	1927- May 1, 1937.	1900- May 1, 1937.	1900-1926.	1927- May 1, 1937.	1900- May 1, 1937.	1900-1926.	1927- May 1, 1937.	1900- May 1, 1937.	1900-1926.	1927- May 1, 1937.
Total, 1900-1935												
All ages . . .	133.8	134.4	295	..	227	121.6	124.5	245	..	198
Under 45 . . .	119.3	132.7	37	..	27	118.8	123.8	32	..	23
45-64 . . .	123.7	122.4	132	..	96	102.9	105.8	100	..	78
65 and over . .	152.2	148.3	126	..	104	146.1	145.4	113	..	97
1900-1926												
All ages . . .	128.5	131.7	126.8	194	68	126	122.0	110.6	126.8	173	47	126
Under 45 . . .	106.3	93.8	119.5	22	10	12	114.2	107.8	119.5	21	9	12
45-64 . . .	112.5	127.2	103.9	86	36	50	100.5	93.6	103.9	72	22	50
65 and over . .	159.7	173.6	155.4	86	22	64	154.4	150.7	155.4	80	16	64
1927-1935												
All ages	145.2	101	120.7	72
Under 45	145.5	15	128.8	11
45-64	151.7	46	109.5	28
65 and over	138.3	40	129.3	33

* Excludes immediate mortality (*i. e.*, patients dying within 1 week of original observation).

These results, based upon the experience as a whole, include many patients who were seriously ill and in whom the glycosuria was an unimportant phase of cardiovascular and renal disease, cancer, hyperthyroidism and other serious conditions. On that account, the mortality in the first year especially was high, and if this is excluded, the results are distinctly more favorable. The mortality after the first year was, at all ages combined, approximately 20% above that expected by the standard tables.

Considered by age, the mortality ratios are generally highest past 65 and lowest between 45 and 64. The level of mortality except at the oldest ages is approximately that existing in substandard insurance risks.

Even the exclusion of the first year cases, however, does not give an accurate picture of the mortality of patients with uncompli-

cated non-diabetic glycosuria. Unfortunately, the data at hand do not permit complete segregation of such cases from those in which the glycosuria was incidental to other diseases. A review of the records, however, shows that a fairly large number had serious complications, such as cardiovascular disease, which would preclude them from insurance of any kind. High also was the incidence of overweight of sufficient degree to warrant limitation of many of these to substandard insurance on that account alone. Under these circumstances, the mortality results, excluding the first year experience, should be regarded as favorable and permit the conclusion that non-diabetic glycosuria in itself has little or no adverse influence on longevity.

Causes of Death. The majority of the deaths among these non-diabetic glycosurics resulted from cardiovascular and renal diseases, and in this group organic heart disease and coronary artery disease accounted for the largest number of deaths. The mortality from cancer was abnormally high, accounting for 19% of the deaths. Various types of infections, such as pneumonia, influenza, appendicitis and gall bladder disease, accounted for 10% of the deaths. No other cause of death was frequent.

In the foregoing, the deaths of those patients subsequently developing diabetes are included under the cause from which they died. The number of patients dying with diabetes was 48, or 15.5% of the total. Nearly two-thirds of the diabetics died of arteriosclerotic disease of the heart, kidney or vascular system. This proportion is distinctly higher than in the experience as a whole. No other single cause of death was prominent among the diabetics. *Not a single death was reported from diabetic coma.* Only 3 deaths were reported as due to diabetes without further details.

Table 15 shows the principal causes of death in the group as a whole. The table also gives the facts separately for those with and without diabetes. It includes 3 deaths discovered subsequent to May 1, 1937, the closing date of the mortality table in the preceding section.

The high mortality from cancer is significant.* Analysis according to site shows that 61% of the cancer deaths were primary digestive-tract cancers. This ratio is definitely above normal. Digestive-tract cancers accounted for 49% of all cancer deaths in the United States during 1932-1936 and for 46% of the cancer deaths among Industrial policyholders of the Metropolitan Life Insurance Company during 1911-1935. The liver was involved in 11 cancer deaths in our series and the pancreas in 7 deaths, of which 5 were primary cancers of the pancreas. Approximately 40% of the cancer deaths occurred within a year of examination, as compared with only 15% for

* There is probably some bias in these data because of the close association of the George F. Baker Clinic with the Palmer Memorial, another division of the New England Deaconess Hospital, which had a relatively high proportion of cancer patients.

all other causes combined. A few of these patients were known to have cancer at first examination, or cancer was then diagnosed.

The proportion of first-year deaths was about the same for digestive and other cancers. Of the 11 deaths with cancer of the liver,

TABLE 15.—CAUSES OF DEATH AMONG PATIENTS ORIGINALLY DIAGNOSED AS NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT DYING FROM SPECIFIED CAUSES. ALL DEATHS AND DEATHS OF PATIENTS BECOMING DIABETIC AND THOSE REMAINING NON-DIABETIC SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Cause of death.	All deaths.		Diabetics.		Non-diabetics.	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
All causes	310	100.0	48	100.0	262	100.0
Cardiovascular and renal diseases, total	171	55.2	31	64.5	140	53.4
Organic heart disease	56	18.2	11	22.8	45	17.2
Coronary artery disease	49	15.8	7	14.5	42	16.0
Chronic nephritis	15	4.8	2	4.2	13	5.0
Cerebral hemorrhage	33	10.6	5	10.4	28	10.7
Gangrene	6	1.9	3	6.3	3	1.1
Arteriosclerosis	12	3.9	3	6.3	9	3.4
Cancer	59	19.0	2	4.2	57	21.8
Diabetes	3*	1.0	3*	6.3
Tuberculosis	6	1.9	1	2.1	5	1.9
Infections, total	32	10.3	7	14.5	25	9.5
Accidents	8	2.6	1	2.1	7	2.7
Suicide	5	1.6	5	1.9
Other and not specified	26	8.4	3	6.3	23	8.8

* No further details.

TABLE 16.—CANCER DEATHS ACCORDING TO SITE AMONG NON-DIABETIC GLYCOSURICS, WITH SPECIAL REFERENCE TO INVOLVEMENT OF THE LIVER AND PANCREAS. DEATHS WITHIN A YEAR OF FIRST OBSERVATION SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900-1937.

Site of cancer.	Number of deaths.	
	Total cases.	First year cases.
Total	59	24
Digestive tract and peritoneum, total	36	15
Esophagus	1	..
Stomach	12	6
Intestines	9	2
Rectum	3	1
Liver	5	2
Pancreas	5	4
Peritoneum	1	..
Breast	6	1
Other and not specified	17	8
Liver, including metastatic	11*	4
Pancreas, including metastatic	7*	5

* One case pancreatic and hepatic involvement, secondary to cancer of stomach.

4 occurred in the first year; and of the 7 with cancer of the pancreas, 5 were first-year deaths.

There were only 2 cancer deaths among patients who became diabetic, one from an "abdominal" cancer 4 years after first observation and 1 from cancer of the colon, 14 years after first observation. The details regarding cancer are given in Table 16.

Discussion. The data of this paper demonstrate that glycosuria of significant degree (over 0.3%), particularly if found on more than one occasion, must not be dismissed lightly. One must remember that these 1,946 patients were part of a much larger group of 14,000 individuals with glycosuria, of whom the vast majority were diagnosed as true diabetics at initial observation. Caution must be taken in diagnosis and advice to the patient, even though random blood sugar values are within normal limits. Usually the glycosuria remains benign; but, nevertheless, of these 1,946 patients, thought at initial observation not to be diabetic, 9.9%, over a period of subsequent observation averaging nearly 9 years, have shown characteristics compatible with the diagnosis of diabetes. Moreover, the probability of the development of diabetes later in life is far greater for these patients than for the population at large.

With individuals, then, exhibiting glycosuria, how can one detect those who have mild diabetes or foretell those who stand the greatest chance of later developing diabetes? This experience affords certain clues. In the first place, the glycosuria is most likely to be significant, if the individual is or has been overweight, if he is over 40 years of age and if he is Jewish. The presence of diabetes in a near relative is of some, though less, importance. In the second place, if random blood sugar values are borderline or slightly above average, the glycosuria takes on added significance. If special studies, such as sugar tolerance tests, are carried out, particularly with individuals possessing one or more of the above characteristics, latent or mild diabetes may be detected in a sizable percentage. Thus the diagnosis was subsequently changed in only 6.3 per 1,000 per annum among those studied with glucose tolerance tests, as compared with 12.6 per 1,000 per annum in patients not "adequately" studied.

Certain aspects of the group with changed diagnosis are significant and reassuring. The diabetes developed by most of these patients is relatively mild. None has died in diabetic coma. Only 73 of the 193 patients have taken insulin at any time up to the present. In some instances, the diabetes was so mild as to be demonstrable only by a sugar tolerance test.

Particularly with individuals in or past middle life, glycosuria may accompany and thus even suggest a degenerative disease of more seriousness than diabetes, so far as duration of life is concerned. Of the 310 deaths in the present series, 65, or over 20%, took place within a year of the first observation usually from such diseases

as cardiovascular or renal disturbances, cancer or infections. In so far as the data permit a conclusion, non-diabetic glycosuria in itself seems to have little or no adverse influence on longevity.

Sugar tolerance tests are fallible. Whether the test be of the standard type using varying amounts of glucose or whether it be of a special variety such as the "one-hour two-dose" tolerance test,¹ the curve must be interpreted in the light of various factors. Carbohydrate tolerance may be temporarily lowered by an infection or toxemia, by starvation or a low starch diet and by the giving of insulin. Furthermore, age has a definite influence. Glycosuria or hyperglycemia may at times be found in various conditions, among which are hypertension, nephritis, pregnancy, hyperthyroidism, diseases of the liver, the pituitary and the adrenals, cancer, gall-bladder disease, obesity and arthritis.

In carrying out tolerance tests, the following points in the technique are essential for dependable results.

1. The sugar solution should be made as palatable as possible and not be of more than 20% concentration. The patient must take the full dose of sugar prescribed, must retain it and not be appreciably upset by the procedure.

2. The test should be done after a fast of at least 5 hours and preferably 12 hours. This conservative minimum has been adopted by the George F. Baker Clinic, because curves at shorter intervals after food may be bizarre and give misleading results.

3. To make certain that no febrile illness exists, the body temperature should be taken before the beginning and after the end of the test.

4. Blood must be collected in such manner as to prevent clotting and as to preserve the sugar content.

5. Tests should be done under competent supervision. More than one unusual result has been traced to a laboratory error. If the result given does not agree with the clinical findings, the test should be repeated.

Melituria Other Than Glycosuria. As an addendum to this presentation, brief comment is necessary regarding those cases of normoglycemic melituria in which the urinary sugar is not glucose but lactose, galactose, fructose or pentose. In every individual with melituria proved not to be diabetic, the type of sugar excreted should be identified with the aid of special tests, including the fermentation test, reduction with Benedict's solution at temperature below 60° C., Seliwanoff's and Bial's tests, and the formation of the respective osazones with characteristic melting points. The series in this paper includes 4 cases of pentosuria and 1 of levulosuria. Such cases are most commonly found among Jewish males. Often the diagnosis of diabetes is made in these patients, then later changed to renal glycosuria and then finally, perhaps after many years have elapsed, the true diagnosis is made. There is, of course,

no connection between these meliturias, other than glycosuria, and true diabetes.

Conclusions. 1. Of 2,065 patients seen from 1900 to 1935 who at first observation were thought to have non-diabetic glycosuria, all but 1.5% were traced as of May 1, 1937. The condition of the patients was ascertained at the time of tracing. After certain exclusions, 1,946 cases remained on which this study was based.

2. Of the total of 1,946 patients, 1,142 are males and 804 females. Living cases number 1,636 and fatal cases 310.

3. In 193 cases (9.9% of the total) true diabetes has developed. In most instances the diabetes was mild. No case of renal glycosuria, as strictly defined above, has progressed to diabetes.

4. Factors favoring diabetes were, in approximately the order named, advancing age, overweight, blood sugar values above the average normal at first observation (though below a definitely diabetic level) and in the younger patients a family history of diabetes. The percentage becoming diabetic rose with increasing duration since initial observation. It was higher in Jewish than in non-Jewish patients.

5. Adequate study at initial observation, particularly with post-prandial blood sugar tests and glucose tolerance tests, increased greatly the chances of distinguishing diabetic from non-diabetic glycosuria.

6. Among 310 fatal cases, 262 deaths were of patients whose glycosuria remained benign, but a significant proportion of these deaths occurred within a year of first visit. Both among those becoming diabetic and those remaining non-diabetic, the incidence of deaths from cardiovascular and renal diseases was strikingly high. The incidence of cancer as a cause of death was five times as high in the non-diabetic as in the diabetic group. There was no death from diabetic coma.

7. Glycosuria, apart from diabetes, may be an accompaniment and a warning sign of degenerative disease and thus be of unfavorable diagnostic import.

8. In the absence of complications, non-diabetic glycosuria seems to exert little or no adverse influence on length of life.

9. Diagnostic standards and procedures, particularly as regards sugar tolerance tests, are discussed.

10. The desirability of recognizing cases of pentosuria and fructosuria is stressed.

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WHY DIABETICS DISCONTINUE PROTAMINE INSULIN.

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THE first 1250 patients of this clinic to take protamine insulin in one form or another between August, 1935 and April 1937, were followed up in the spring of 1938 and 1222 (97.7%) were traced. A preliminary report of the results of a study of these cases has already been made^{1a} and a second paper will be given soon.^{1b} Of the entire group, 102 had discontinued protamine insulin, 7 of them temporarily. To analyze their reasons for giving up protamine insulin is the object of this paper. The data are given in detail below.

TABLE 1.—REASONS FOR ABANDONING PROTAMINE INSULIN.

Reason.	Patients.	
	No.	Per cent.
Sugar-free without insulin	41	43.1
Hypoglycemic reactions	33	34.7
Local allergic responses	3	3.1
Uncoöperative	5	5.3
Poor diabetic control	5	5.3
Advice of home physician	4	4.2
Irregular mode of living	2	2.1
Insufficient time for adjustment	1	1.1
No reason apparent	1	1.1
	95	100.0
Discontinued, later resumed	7	
	102	

Seven patients who gave up *protamine zinc insulin* for one cause or another are now using it again. It must be remembered, particularly with regard to the patients who started it in 1935, that protamine insulin was then a new discovery and its effects were inadequately understood. Thus, one of the diabetic children was originally adjusted to *protamine zinc insulin* at a summer camp and went from there to the Philippine Islands. Her mother did not receive instruction in the management of diabetes such as she would have received had her daughter been in the hospital. The child had severe hypoglycemic reactions and the mother shifted her back to unmodified insulin. This summer the patient has been at a diabetic camp again for several weeks, receives *protamine zinc insulin* along with the rest of the youngsters and has been well and free from reactions.

The largest number of the group, 41, is made up of those who are sugar-free without insulin when on a careful diet and under normal circumstances. A few of them take small quantities of insulin occasionally, but most of them get along well without it.

Hypoglycemic reactions with *protamine zinc insulin* are responsible for the largest group of diabetics, 33, who have resumed regular (unmodified) insulin. The symptoms have varied in severity from mild, constant fatigue, headaches, nervousness or nausea to rare complete unconsciousness. This group includes both mild and severe diabetics. Most of these 33 patients write that they are happier and freer from reactions now that they have returned to the old insulin. Many of them state that they varied between marked glycosuria and hypoglycemic reactions and add that if they took enough insulin to clear up the urinary sugar, reactions ensued. Many of them found that the insulin shock with protamine insulin was more severe than with regular insulin. Of the 78 deaths (among the total of 1250 cases) reported up to June 9, 1938, however, none seemed to their home physicians or the writer to be attributable to *protamine zinc insulin*.

In 3 cases, local allergic responses, painful and indurated areas at the site of injection, caused patients to discontinue protamine insulin. In no instance, except in one doubtful case, did an abscess result.

It was impossible to secure the coöperation of 5 patients. Two of this number were definitely psychotic and it was felt that the other 3 were too unintelligent to learn how to use the new preparation properly.

Another group of 5 patients were definitely able to control their diabetes better with the old insulin than with *protamine zinc insulin*. It is possible, however, that even with these patients hospitalization and careful study might enable one to control their diabetes with protamine insulin or with a combination of regular and protamine.

Four diabetics were changed back to regular insulin because their local physicians believed it preferable in their particular cases. Another 2 patients lead irregular lives, changing back and forth from day to night work and are better controlled on the old insulin. One patient was started on *protamine zinc insulin* at the hospital but left before the adjustment had been satisfactorily made. In one case no reason for discontinuing *protamine zinc insulin* was apparent.

Discussion. It is evident from the above that if those patients are excluded who now require no insulin for control of diabetes and those who later resumed protamine insulin, only 54 (4.4%) of the 1222 traced have discontinued the slowly acting preparation. Of these 54, 5 were uncoöperative and others gave it up for reasons which seem inadequate. Furthermore, experience gained during the past 3 years has demonstrated that hypoglycemic reactions, which led 33 patients to discontinue protamine insulin, need be no more frequent, if as frequent, with the new as with the unmodified insulin. Avoidance of reactions is achieved in almost all cases by recognition of the fact that when one uses *protamine zinc insulin* once daily

before breakfast, a normal fasting blood sugar value precludes further increase in dosage. If more insulin is needed to control hyperglycemia during the course of the day, the unmodified type must be used. In almost all cases, this may be given as an accompaniment of the protamine insulin before breakfast with no more insulin of any sort during the rest of the day. The blood sugar value in the late forenoon serves as an index of the effect of the unmodified insulin.

Conclusion. At the very outside, therefore, the number of diabetic patients who cannot use *protamine zinc insulin* successfully and to great advantage is less than 5%; and, allowing for the factors discussed above, is probably much less than this low figure. Certainly we should not withhold protamine insulin from the great mass of diabetics merely because an occasional patient seems not to do well with its use.

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(1.) Joslin, E. P.: (a) J. Am. Med. Assn., 109, 497, 1937; (b) Protamine Insulin; paper read at Gesellsch. f. Verdauungs. u. Stoffwechselkrankh., Stuttgart, September 22, 1938.

BOOK REVIEWS AND NOTICES.

THE RHEUMATIC DISEASES. A Course of Lectures Arranged by The Medical Staff of the St. John Clinic and Institute of Physical Medicine. Edited by SIR LEONARD HILL, M.B., LL.D., F.R.S., Director of Research, St. John Clinic and Institute of Physical Medicine and Consultant to the Rheumatic Unit at St. Stephen's Hospital (London County Council), and PHILIP ELLMAN, M.D., M.R.C.P., Physician to St. John Clinic and Institute of Physical Medicine and Consultant to the Rheumatic Unit at St. Stephen's Hospital (London County Council). With a Foreword by SIR ARTHUR MACNALT, K.C.B., M.D., F.R.C.P., Chief Medical Officer to the Ministry of Health. Pp. 270; 46 illustrations. Baltimore: William Wood & Co., 1938. Price, \$4.00.

THIS book is a symposium by 15 contributors; as explained by the Editor in the preface it is based upon a "course of weekly lectures on Rheumatic Diseases. . . . In a volume of this kind, written by individuals on closely related subjects, some degree of overlapping is inevitable . . . any divergence of opinion observed by the reader is not without merit in the present limited state of our knowledge." The book is divided into 20 chapters or articles, exclusive of the foreword, covering such topics as the social and economic aspects of Rheumatic Diseases, classification, pathology, focal infection, radiology, serology, non-articular rheumatic affections and treatment. For the most part, the views expressed are those familiar to readers of the American literature on the subject. The articles show a trend of opinion toward the view that rheumatic fever and rheumatoid arthritis are different forms of the same pathologic process. The infectious nature of "rheumatoid arthritis" seems to be conceded by most of the contributors, with due appreciation of other etiologic factors involved. A few of the opinions expressed are a little startling; for instance, C. A. Robinson says "I hold that chronic infective arthritis in women is due, in the vast majority of cases, to an infected cervix." Fibrositis is described as a very common condition, but the explanation of its pathologic physiology is rather vague. The section on physical therapy comprises nearly a quarter of the book. The importance of orthopedic treatment is stressed but detailed descriptions are necessarily lacking; the beneficial results of arthrotomy and lavage are repeatedly mentioned.

The paper, print and illustrations are good. This little book is, in general, both sound and pleasant. However, the Reviewer believes that it does not fill any important need of American readers; as a review course for either the general internist or the family practitioner, he prefers the summaries of current literature on arthritis and allied diseases which are published annually in periodicals.

J. C.

PEDIATRIC SYMPTOMATOLOGY AND DIFFERENTIAL DIAGNOSIS. By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post Graduate School. Pp. 500; 29 illustrations, including 1 colored plate. Philadelphia: F. A. Davis Co., 1938. Price, \$5.00.

USING terse, direct sentences, the author presents the symptoms and physical features of the multitudinous ailments of children. Etiology,

pathology, prophylaxis and therapeutics are as a rule not touched upon. Roentgenology and clinical laboratory methods receive brief and inadequate mention. Some illustrations are included. The index consists mainly of the names of diseases; symptoms are listed but rarely. The usefulness of this volume appears restricted to those fact-loving physicians who desire a handy volume in which they can look up the information there contained.

I. W.

MARIHUANA. AMERICA'S NEW DRUG PROBLEM. A Sociologic Question With Its Basic Explanation Dependent on Biologic and Medical Principles. By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. With a Foreword by E. M. K. GEILING, Professor of Pharmacology, University of Chicago, and a Chapter by FRANK R. GOMILA, Commissioner of Public Safety, New Orleans, and M. C. GOMILA LAMBOU, Assistant City Chemist. Pp. 223; 13 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, \$3.00.

WHAT to the farmer is known as a weed, in history is known as hashish, in medicine as *cannabis sativa*, and in an Act of Congress, as marihuana. This monograph, which is a fair appraisal of the marihuana problem, shows that titles such as the "Flower of Hell" and "Marihuana—Assassin of Youth," suggest capacity for harm that are misleading. Some of the contents of the volume describe the history of the hashish vice and its distribution; present status of the vice in the United States; botanical consideration; hashish experience includes literary, subjective, objective and psychiatric descriptions; acute and chronic effects; therapeutic applications; pharmaceutical and chemical considerations. So unpredictable is its action, that marihuana has been called "the coquette of drugdom." Plants growing side by side may vary vastly in potency; when all other conditions are the same, the effects upon 2 persons may be opposite, and upon the same person, they may differ greatly at different times. Our own Bayard Taylor, who desired first-hand information, while once in the Orient, decided to learn the subjective effects of hashish; by mistake, six times the usual quantity was taken, and his description of its acute effects is a classic; full recovery testifies to the frequent statement that there probably are no authentic instances of fatalities. Marihuana's fame as an aphrodisiac is not fully justified. With us, indulgence is usually in the form of cigarettes, known in the vernacular as "reefers;" the smoke is always inhaled and retained for considerable time. The smoker is usually aware of increasing energy and power; often there is excitement, with the user realizing that his thoughts and actions are coming less under control; faces of those about may assume grotesque expressions, or the subject may be seized with unprovoked laughter, realizing at the time its ridiculousness; lengthening of time and space is usually experienced, and double consciousness may be present. Its use does not enslave as does opium; if one speaks of the latter as causing addiction, perhaps one should say the use of marihuana leads to habituation. Its relation to crime is similar to that of alcohol, neither producing crime directly, but through releasing inhibitions, tendencies usually under restraint may then become active. After preparations of marihuana have been smoked, or ingested, daily in large quantities, and over long periods of time, its users show some degree of permanent mental impairment. There is a classified bibliography of more than 17 pages, an extensive author index and an informative general index.

N. Y.

AVIAN TUBERCULOSIS INFECTIONS. By WILLIAM H. FELDMAN, D.V.M., M.S., Associate in Division of Experimental Medicine, Institute of Experimental Medicine; Associate Professor of Comparative Pathology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 483; 109 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, \$7.00.

As the author states in his preface, avian tuberculosis, except by those especially interested in comparative medicine, is a poorly understood field. Veterinarians are well acquainted with its practical aspects; practising physicians, on the other hand, are almost unacquainted with the problem or the light that its understanding can throw on the general problems of tuberculosis. This book—written in order to provide a convenient source of knowledge of avian tuberculosis, useful alike to veterinarians, experimental pathologists, teachers and physicians—successfully fulfils its purpose.

The monograph opens with an interesting review of the extent and importance of avian tuberculosis, which is a major hazard in an industry valued at \$2,000,000,000 annually in the United States. While the disease is widely distributed throughout the country, its greatest concentration occurs in the north central states, where about 50% of flocks and 3 to 6% of chickens are infected.

The book proceeds, with good organization and an easy, clear style, to chapters on laboratory procedures in the understanding of avian tuberculosis, the pathology of the disease, the pathogenicity of the avian bacillus, and the control of its dissemination. A bibliography is attached to each chapter.

The section on laboratory methods is notable in combining an excellent review of the subject in broad aspect with explicit instructions for the important procedures of isolation of the bacillus, typing for pathogenicity and tuberculin testing. The chapters on the pathologic anatomy of avian tuberculosis in its spontaneous and experimental forms are comprehensive and well illustrated.

The chapters on the pathogenicity of the avian tubercle bacillus for the various animal species are among the most valuable, for it is in this field that general knowledge is most lacking. The important question of pathogenicity for swine is discussed at length, with its bearing on the epidemiology of the disease in chickens. Naturally physicians will be especially interested in Feldman's review of the reported cases of avian bacillus infection in man. He lists 37 reported cases, but regards not more than 13 as valid. As he states, in view of man's opportunity for infection, the rarity with which he develops lesions indicates a formidable resistance. Feldman considers the evidence of an etiologic rôle of the bacillus in Hodgkin's disease quite unconvincing.

A final chapter appropriately takes up the subject of control of dissemination of the disease in poultry.

E. L.

CLASSIC DESCRIPTIONS OF DISEASE. With Biographical Sketches of the Authors. By RALPH H. MAJOR, M.D., Professor of Medicine, University of Kansas School of Medicine. Pp. 727; illustrated. Second edition. Springfield, Ill.: Charles C Thomas, 1939. Price, \$5.50.

THE second edition of this excellent medical anthology is especially welcome as enough new material is included to make it distinctly more valuable than the first. It has proved possible, without greatly increasing the size of the book, to include 27 more original accounts by 11 more authors than in the first edition. Among the most important are 9 descriptions of malaria, ranging from Aristophanes to Ronald Ross, the Yellow Fever

accounts of Matthew Carey, Benjamin Rush, Carlos J. Finlay and Walter Reed; W. S. Kirkes' account of pyemia resulting from (subacute bacteria) endocarditis; Koplik's spots; Heberden's nodes; a case of allergy from Jenner's *Inquiry*; and parts of Withering's account of foxglove. New Lives and Illustrations are equally in evidence, so that it becomes ungracious to wish that still others might have been included that now remain conspicuous by their absence! Except for a good textbook of medical history, we know of no single volume on the subject that should be more interesting or instructive to physicians of all kinds. Readers should not be confused by the accidental omission of the title "Plague" and of references to Thucydides and Rufus in the Table of Contents.

E. K.

CARDIOVASCULAR DISEASE IN GENERAL PRACTICE. By TERENCE EAST, M.A., D.M. (OXON.), F.R.C.P. (LOND.), Physician and Physician-in-Charge of Cardiological Department, King's College Hospital; Physician, Woolwich War Memorial Hospital, etc. Pp. 206; 43 illustrations. London: H. K. Lewis & Co., Ltd., 1938. Price, 10s. 6d; Philadelphia: P. Blakiston's Son & Co., 1939. Price, \$3.50.

This little book is one of a series issued by the publishers, called "The General Practice Series. The subject is as completely covered as could be expected in a book of this size. It is recommended for those practitioners who wish to consult an elementary discussion of cardiovascular disease. In the opinion of the Reviewer, however, it is a little too elementary, and does not include enough discussion of the details of treatment, to be useful to most American practitioners.

C. W.

THE SURGERY OF ORAL AND FACIAL DISEASES AND MALFORMATIONS. Their Diagnosis and Treatment Including Plastic Surgical Reconstruction. By GEORGE VAN INGEN BROWN, D.D.S., M.D., C.M., F.A.C.S., Emeritus Professor of Plastic Surgery, University of Wisconsin; Plastic Surgeon, Children's, St. Mary's, Columbia, and Milwaukee County Hospitals, Milwaukee; State of Wisconsin General Hospital, Madison, etc.; Colonel, Inactive Reserve, United States Army. Pp. 778; 589 engravings containing 1019 illustrations and 12 colored plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

EACH successive appearance of this work, which was first published in 1912, reflects the great strides that have been made in the surgery of this part of the body over a period of about 25 years. The book is not limited to surgery, but covers also many of the manifestations of skin and general diseases about the face and mouth. With few exceptions, the views expressed in this section are in accord with accepted teaching. In the treatment of erysipelas and actinomycosis, it is surprising to note that no mention is made of irradiation. The chapter on tumors of the mouth and jaws, and especially the section dealing with the growths arising from dental issues, cannot be said to be well systematized, and is likely to be confusing to the student.

The author's wide experience with harelip and cleft palate fully justifies the space devoted to this subject. In general, his views on the principles of treatment of this deformity are in accord with those of most present-day surgeons in this field. He discusses at length the advantages of the "bone-flap operation" in cleft palate as compared to the use of mucoperiosteal flaps alone.

In this fourth edition the chapters on plastic surgical restoration of facial deformities form a noteworthy contribution to the literature of the subject, and are perhaps the outstanding feature of the book.

R. I.

SURGICAL PATHOLOGY OF THE DISEASES OF THE MOUTH AND JAWS. By ARTHUR E. HERTZLER, M.D., Surgeon to the Agnes Hertzler Memorial Hospital, Halstead, Kansas; Professor of Surgery, University of Kansas. Pp. 248; 206 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, \$5.00.

THIS is the last of the author's 10 volumes on surgical pathology; in his characteristic phrase, "after thirty-five years of writing I shall trade my pen for a lollipop." He recognizes difficulties with his subject, especially for the two reasons that this field has moved from the hands of "general practitioners like myself" to those of specialists and dentists; and also because he is forced to describe many things that he has not seen. In regard to the literature, he has "adopted the more respected practice of having my secretary copy them out of the Cumulative Index!"

E. K.

NEW BOOKS.

Elementary Anatomy and Physiology. By JAMES WHILLIS, M.D., M.S., F.R.C.S., University Reader in Anatomy, Guy's Hospital Medical School; late Lecturer in Anatomy in the University of Durham. Foreword by T. B. JOHNSTON, M.D., CH.B., Professor of Anatomy, University of London. Pp. 342; 87 illustrations, prepared from original drawings by Pauline Larivière. Philadelphia: Lea & Febiger, 1939. Price, \$3.50.

The Patient is the Unit of Practice. By DUANE WILLARD PROPST, A.B., B.S., M.D., Assistant Professor of Medicine, University of Illinois College of Medicine. Pp. 219; 4 plates. Springfield, Ill.: Charles C Thomas, 1939. Price, \$3.50.

The Diagnosis and Treatment of Diseases of the Thyroid. By JAMES H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital, and EDWARD P. RICHARDSON, M.D., John Homans Professor of Surgery, Harvard University, and Chief of the West Surgical Service (Massachusetts General Hospital). (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 367; 51 illustrations. New York: Oxford University Press, 1938. Price, \$5.00.

Fluorine Toxicosis in the Albino Rat. (Research Bull. 247, Agricultural Experiment Station, Iowa State College of Agriculture and Mechanic Arts). By J. A. SCHULZ. Pp. 242; 1 figure and 28 tables. Ames, Iowa: Iowa State College of Agriculture, 1938.

Ueber die Integrative Natur der Normalen Harnbildung, Teils I, II, III (Teil III. Systematischer Rückblick). By GÖSTA EKEHORN, D.R. Med., Stockholm. Pp. 1429. Helsingfors: Printed by Mercators Tryckeri, 1938.

Proceedings of Meetings of the New York Pathological Society held October 28, November 18 and December 23, 1937; January 27, February 24, March 29, April 28 and May 26, 1938. (Reprinted from Archives of Pathology.) Pp. 46; 2 illustrations.

Clinical and Experimental Investigations in Agranulocytosis. With Special Reference to the Etiology. By PREBEN PLUM. Pp. 410; 125 illustrations, many in color. London: H. K. Lewis & Co., Ltd., 1937.

Die endokrinen Drüsen des Gehirns, Ephyphyse und Hypophyse. Ein Blick in ein interessantes Gebiet. By DR. MED. PAUL NIEHANS, Chirurg. F. M. H. der Klinik von Clarens und der Spitäler von Vevey und Montreux (Schweiz). Pp. 280. Bern: Medizinischer Verlag Hans Huber, 1938. Price, Fr. 10.50.

- St. Thomas's Hospital Reports*, Second Series, Vol. III. Editors: Prof. O. L. V. S. DE WESSELOW, MR. C. MAX PAGE, assisted by MR. N. B. BARRETT, DR. J. ST. C. ELKINGTON, DR. A. J. WRIGLEY. Pp. 240; many illustrations. London: Headley Brothers for St. Thomas's Hospital, 1938. Price, 7s. 6d. (after publication 10s. per volume).
- William B. Wherry, Bacteriologist*. By MARTIN FISCHER. Pp. 293; 21 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.00.
- Surgical Treatment of Hand and Forearm Infections*. By A. C. J. BRICKEL, A.B., M.D., Departments of Anatomy and Surgery, Western Reserve University. Pp. 300; 166 illustrations and 35 plates (10 in color). St. Louis: The C. V. Mosby Company, 1939. Price, \$7.50.
- Richtlinien Praktischer Orthopädie*. By DR. ALBERT LORENZ. Pp. 464; 123 illustrations. Wien: Franz Deuticke, 1939. Price, Paper, M. 15; Bound, M. 16.80.
- Recipes and Menus for Allergics*. By MYRA MAY HAAS. In Collaboration with NATHAN SCHAFER, M.D. Menus by CAY HILLEGAS. Illustrations by O. SOGLOW. Pp. 250; illustrated. New York: Dodd, Mead & Co., 1939. Price, \$2.50.
- Medicine in the Outpatient Department*. An Introductory Handbook. By WINTHROP WETHERBEE, JR., M.D., Junior Visiting Physician, Boston City Hospital. With a Foreword by GEORGE R. MINOT, M.D., S.D., F.R.C.P. (EDIN. and LON.), F.A.C.P., Professor of Medicine, Harvard University; Director, Thorndike Memorial Laboratory; Visiting Physician, Boston City Hospital. Pp. 111. New York: Paul B. Hoeber, Inc., 1938. Price, \$1.00.
- Cardiovascular Disease in General Practice*. By TERENCE EAST, M.A., D.M., OXON., F.R.C.P. LOND., Physician and Physician-in-Charge of Cardiological Department, King's College Hospital; Physician, Woolwich War Memorial Hospital, etc. Pp. 206; 43 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, \$3.50. (Review p. 563).
- Clinical Bacteriology*. By F. A. KNOTT, M.D., M.R.C.P., D.P.H., Director, Bacteriological Department and Lecturer in Bacteriology, Guy's Hospital. Pp. 426; 60 illustrations, including 12 plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, \$4.50.
- Consolidated Indices*. Embracing Transactions of the American Roentgen Ray Society (1903-1908); American Quarterly of Roentgenology, Vols. I-V (1906-1913); American Journal of Roentgenology, Vols. I-IX (1913-1922); American Journal of Roentgenology and Radium Therapy, Vols. X-XXXVIII (1923-1937). Author and Subject: 1903-1937. Compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society, 1939. Pp. 451. Springfield, Ill.: Charles C Thomas, 1939. Price, \$12.50.
- The New International Clinics, Vol. I, N.S. 2, 1939*. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine University of Pennsylvania, Philadelphia. With 18 Collaborators. Pp. 312; illustrated, also 1 colored plate. Philadelphia: J. B. Lippincott Company, 1939.
- The current number contains 15 original contributions on a variety of subjects, together with clinics from Dr. Eliason's and Dr. Lee's service, and a review of recent progress on water balance; edema and dehydration by Cantarow.
- Bacteria. The Smallest of Living Organisms*. By DR. FERDINAND COHN (1872). Translated by CHARLES S. DOLLEY (1881). Introduction by MORRIS C. LEIKIND. Pp. 44; 4 illustrations. Baltimore: The Johns Hopkins Press, 1939. Price, \$1.00.

PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF
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PROLAPSE OF THE UTERUS.

ALTHOUGH uterine prolapse has been recognized and treated since the days of prehistoric woman, it has only been within recent years that gynecologists have seriously studied the causes of this condition and outlined rational methods of treatment. There are so many theories concerning the mechanism of uterine support that Mengert¹³ has attempted a quantitative evaluation of the relative importance of the various uterine supports. He took 8 female cadavers, none of which had uterine prolapse and after attaching a 1-kg. weight to the cervix, the paired structures attached to the uterus were severed in varying sequences and the resulting uterine descent measured. It was found that section of the round, ovarian, infundibulopelvic and the upper third of the broad ligaments hardly affected the position of the uterus in the pelvis. The pelvic floor, although it was never incised, did not hinder experimental prolapse of the uterus, and therefore could not have contributed to uterine support in any of the 8 subjects. Section of the parametrial and upper two-thirds of the paravaginal tissues allowed an average uterine descent of 10.5 cm. Marked descent of the uterus amounting to actual prolapse never occurred so long as any part of the upper two-thirds of the paravaginal or lower two-thirds of the parametrial tissues were intact and of these two tissues the paravaginal tissue seemed to be slightly more important, for its division allowed an average uterine descent of 6.9 cm. as compared with 3.6 cm. following division of the parametrial tissues. These paravaginal structures which are so important are also known as cardinal ligaments and are of great importance in the operative correction of prolapse as will be discussed later.

Although injury to the paravaginal tissues is of great importance in the etiology of prolapse, it does not explain the instances of prolapse

in nulliparous women or even virgins in whom there has never been any vaginal trauma. As a result of some study which Laws¹¹ has made, he believes that in many of these cases there is a spina bifida occulta, which involves the fourth sacral nerve with consequent paralysis of the levator ani muscles. This condition may also account for early recurrence of prolapse after operation, as he found in 3 of his cases. He states that in these cases the symptoms of prolapse may be absent until adult life and then be considered as entirely due to child-birth injuries.

The surgical management of prolapse has been well outlined by Phaneuf,¹⁵ who states that three factors determine the method of operation to be chosen in the given individual, namely, the age of the patient, the possibility of future pregnancies and finally, the extent of the prolapse. Uterovaginal prolapse in young women during the child-bearing age may be satisfactorily treated by repairing the cervix, the anterior and posterior vaginal walls and the perineum, by shortening the uterosacral ligaments and by performing a round ligament suspension of the uterus. After the menopause one of the vaginal methods is given the preference because of increased operability because of lessened morbidity and mortality. An abdominal incision is made in only a limited number of cases, to obliterate a very large posterior vaginal hernia. The interposition operation (Watkins-Wertheim) followed by amputation of the cervix has given him excellent results and has been his favorite method of treatment, but we will have more to say about this operation later. Vaginal hysterectomy with interposition of the united broad ligaments is reserved for women with atrophied uteri and when malignancy is suspected. In feeble old women, where an extensive vaginal operation is contraindicated, either total colpectomy or the subtotal operation of LeFort may render great service, especially when performed under local anesthesia. It is important that an adequate repair of the pelvic floor be made in all cases except in nulliparous women where the perineum is intact and gives good support. Having thus outlined the general principles in the selection of a suitable operation, it will be of interest to discuss in more detail some of the more common procedures.

Manchester-Fothergill Operation. This operation which was devised by the Manchester group of gynecologists and popularized by Fothergill is based primarily upon shortening the cardinal ligaments by reefing them anterior to the uterus by a vaginal approach. It is curious that this operation has been done for years in England with satisfactory results, but has only recently been taken up in our country. From a survey of the literature it is apparent that it is being widely employed and, on the whole, the results have been quite satisfactory. Shaw¹⁸ reports a series of 549 cases in which this operation produced cures in 95%. Being from Manchester his article can be considered authoritative concerning the proper technique of the operation, which will not be discussed in detail in this review, but which should be consulted by those who intend to perform the operation without previous experience. He believes that the operation is the best one for all patients with prolapsus, whether young or old, nulliparous or parous and it is not followed by any difficulty in subsequent labors. The prolapse may recur after subsequent labors in less than 25% of the cases. He says

that it is necessary to combine an abdominal operation with the colporrhaphy only in those very rare cases where practically no muscular tissue is found in the pelvic floor and in his series it was used only in 2 cases. Salmon¹⁷ reports a series of 254 cases in which this operation was used, with only 1 recurrence. In 15 cases there was considerable sagging of the anterior vaginal wall but even in these the cervical stump and fornices remained high up during straining. The operation was put to its severest test in the cases of recurrent prolapse following the interposition operation and ventrofixation and in a group of 8 cases of prolapse of the cervical stump occurring after supravaginal hysterectomy. The universally excellent results in this group were very gratifying. While the English schools feel that the operation is no contraindication to subsequent pregnancy, he believes that pregnancy should be avoided, and it has been his practice to ligate the Fallopian tubes through the vagina in those patients who are still menstruating. In a series of 152 cases reported by Gordon,¹⁹ amputation of the cervix was not done in 50 of them, although this is usually considered a part of the operation. Local anesthesia was used almost routinely after preoperative medication with barbiturates and morphine and in this way it was not necessary to reject poor risks. He has found that slight bleeding about the sixth or seventh day and a foul vaginal discharge are commonly seen and he had 8 cases which were complicated by pelvic cellulitis. Every patient in the series was cured of her prolapse after at least a 2-year observation, although in a small number there were slight residual symptoms which could usually be cured by a minor operation. Even if those with minor symptoms were classified as failures, the curability rate in this series was over 96%. Four patients have had 1 baby since the operation and 2 have been delivered twice; in 1 of these when the rigid cervix was cut, delivery was prompt and spontaneous and her next delivery was easy. In all of these cases the perineum was cut or torn, but the prolapse did not recur. As a result of his experience, he is convinced that no abdominal operation is necessary for the cure of prolapse and since the parametria may be united in the midline without removal of the uterus, hysterectomy is unnecessary but should be reserved for those patients in whom the uterus is diseased.

In discussing the mechanics of the operation, Frank^{7a} is of the opinion that the amount of shortening obtained by amputation of the cervix and suturing the parametria together does not account for the resulting fixation of the cervical tissues. He believes that the favorable result is obtained by condensation and shrinking of the parametrial elastic and connective tissues due to the aseptic trauma occasioned by the operation and resembling to some degree the fixation noted after infection of the parametria, the sole difference is that the scars obtained after the operation are resilient and entirely painless, while the opposite results after inflammation. In his experience the morbidity of the operation has been slight and there has been no mortality. His series includes 60 cases of first-degree prolapse, 30 cases of second degree, 14 cases of third degree and 3 cases of prolapse of the cervical stump, and in the entire series there was only 1 recurrence. He feels that the operation fulfills the requirements of a readily learned operative technique, applicable to a wide range of conditions, which

has proved more satisfactory than vaginal hysterectomy and avoids an abdominal incision with its possible sequelæ.

Interposition Operation. The operation known as the interposition procedure, with which the names of Watkins, Wertheim and Schauta are associated, consists of elevation of the bladder from the vaginal approach and supporting it by placing the fundus of the uterus between it and the vagina. By this means the uterus is interposed between the bladder and vagina and acts as a permanent pessary of autogenous tissue. It is an operation which is usually easy to perform and if used only in properly selected cases gives excellent results. The indications for the operation which are generally accepted are that the patient should be past the menopause with a large cystocele as the chief complaint, the uterus should be neither too large nor too small to act as an efficient vaginal plug and the uterosacral ligaments should be strong enough to hold the cervix well up in the pelvis. Many gynecologists disregard one or more of these factors, and for that reason obtain inferior results with the operation. With an experience of over 500 cases, Rongy, Tamis and Gordon¹⁶ are well satisfied with their results and have extended the field for the operation by performing sterilization as a part of the procedure in those women who have not reached the menopause but have had enough children to suit their desire. They admit that there is a temporary disturbance of bladder function after the operation but this soon corrects itself as the bladder adjusts itself to its new position. They believe that no other operation corrects the displaced organs and cures the pelvic ptosis as does this one and at the same time preserving function so far as menstruation is concerned. They state that the operation is successful because fixed structures are used for support. The uterus acts as a shelf to hold the bladder and is elevated in the pelvis by being tipped forward.

A very interesting report has been made by Baer, Reis and Laemle³ of two series of cases of over 200 patients in each series. In the first group the interposition operation was used as the operation of choice, and in order to see if results would be improved vaginal hysterectomy was employed in the second group as the preferable operation. In both series the patients were operated upon by the same group of gynecologists and it may be assumed that they were equally competent to perform either operation. They found that the interposition operation was completely successful in nearly 90% of the cases, whereas vaginal hysterectomy, to which they turned in order to improve their results, was successful in only 70%. As a result of this comparative study, it is their intention to again avail themselves of the interposition operation as a cure for prolapse of the uterus whenever the conditions for its selection are met. Vaginal hysterectomy will be used by them only in those cases of prolapse in which the uterine disease calls for hysterectomy. In women in whom childbearing is to be conserved they use the Manchester operation for prolapse of the first and second degree, while in third-degree prolapse they employ vaginal plastic reconstruction combined with a ventrosuspension.

A study of the sequelæ after the interposition operation has been made by Dannreuther,⁶ which should be most interesting to any gynecologist who performs this operation. A number of patients complained of the onset of bladder annoyances long after their dis-

charge from the hospital and were found to be suffering from chronic trigonitis. Cystoscopic examination discloses an elevation and marked congestion of the trigone, with small depressions on either side, suggesting that the operator neglected to mobilize the bladder sufficiently in a lateral direction before pulling the uterus forward. He had 3 patients who complained of marked frequency of urination with tenesmus in whom vesical calculi were found. One had calculi in each of two lateral depressions of the bladder, another had a stone in a large posterior pocket behind the underlying uterine body, and the third had multiple concretions in both lateral and posterior areas. In all cases the urine was extremely turbid and loaded with colon bacilli. Vesical calculi are quite rare in the female since drainage is usually excellent, but in these cases the operators not only failed to mobilize the bladder sufficiently but 2 of them had also sutured the cut edge of the uterovesical fold of peritoneum too far back on the posterior surface of the uterus, thus fixing the floor of the bladder at a level below that of the trigone and creating a posterior pocket which tends to harbor residual urine with the later development of stones. In passing, it might be mentioned that the Reviewer has omitted this step of the operation for years with no adverse results and no pocket formation.

Incontinence of urine may be a symptom before operation and cured by it or the lack of control may persist after operation. The relief of this disturbance can almost be assured by preceding the major steps of the operation with a Kelly plication of the vesical sphincter. Since pregnancy is a highly undesirable sequel, he strongly urges against performing the operation in the childbearing woman. If, however, the operation is done combined with a bilateral tubal resection, as advised by some operators, it is important to do a thorough curettage in order to remove a possible attached fertilized ovum.

He has noted three types of postoperative vaginal protrusion, coming on as early as 10 months or as late as 7 years after operation. The first type is a reverse prolapse with bulging of the vaginal wall covering the overlying fundus. The descent of the uterus is exaggerated when the patient strains and it seems to be trying to dive "head first" out of the vagina. This is due to the fact that the fundus was not firmly fixed by stitching the cornu on each side to the periosteum under the pubic arch. The second type is that in which there is really a recurrence of the prolapse, the uterus breaking away from the vaginal wall as a result of defective suturing. The third type is an apparent postoperative bulging of the vaginal mucosa when insufficient tissue has been resected laterally in trimming the flaps. All of these defects are a source of discomfort to the patient and create the impression of an operative failure. Three patients who had been subjected to interposition operations later sought relief from severe menorrhagia due to fibroid tumors of the uterus. Such cases are a further argument against the use of the operation in women who have not reached the menopause. The development of new fibroid tumors is certainly uncommon after menstruation ceases, whereas the activation and enlargement of small intramural nodules is not unusual at any time before then. When fibroids are present at the time of operation, he believes that hysterectomy is always preferable to the interposition operation.

In order to overcome the weakness of the interposition operation in

cases where the uterosacral ligaments are overstretched, Chaffin⁵ has described an operation which he terms a "vaginal subtotal." If the uterosacral ligaments are not strong, although the bladder will be retained by the operation, the uterus will slide down under the bladder at a subsequent time. To overcome this possibility, he performs a subtotal hysterectomy by the vaginal route and places the remaining cervical stump under the mobilized bladder. He then anchors the round and broad ligaments into a scarified area of the posterior vaginal wall just below the stump of the uterus, thus suspending the stump by structures which simulate the action of the uterosacral ligaments. He has performed the operation in more than 50 cases with entire satisfaction.

Vaginal Hysterectomy. In advocating vaginal hysterectomy for the cure of prolapse, Goff⁸ states that the uterus is maintained at a normal level in the pelvis by the visceral part of the fascia endopelvina, especially by those parts of the fascia which are termed the transverse cervical or cardinal ligaments. The basic cause of prolapse is either a congenital defect in or an injury to these ligaments; therefore a successful operation for prolapse must be based on a shortening of these ligaments. He believes that the advantages of vaginal hysterectomy over other forms of operative correction are: 1, it facilitates the shortening of the cardinal ligaments; 2, it facilitates the correction of the abnormalities of the pouch of Douglas; 3, it removes a uterus which is either useless or abnormal in over 80% of the cases; and, 4, it removes the future possibility of neoplastic disease of the uterus. The operation should be used only in patients past the menopause whose physical condition warrants a major surgical procedure and in younger women who have the more marked degrees of prolapse or prolapse associated with pathologic lesions in the uterus. By employing the Bissell type of vaginal hysterectomy he has successfully treated prolapse of the uterus in 98% of his cases.

Colpocleisis. The word "colpocleisis" means occlusion of the vagina and as practised surgically by the gynecologist it may be subdivided into two types, namely, partial occlusion as typified by the LeFort operation and total occlusion which is also called colpectomy. In the opinion of Simon¹⁹ this operation has fallen into an undeserved oblivion in this country largely because it involves the complete anatomic and physiologic loss of the vagina. However, simplicity of performance, safety, uniformly good results and applicability to conditions not amenable to any of the reconstructive types of operation insure for it a permanent place among useful operations. Prolapse in the aged constitutes the most frequent indication for this procedure since it may be done in a short time under local anesthesia. There can be little objection to the loss of the vagina after the age of 70, while the menopause would probably mark the limit below which the operation would be contraindicated. Between these limits he believes that the selection of the operation would depend on the social status of the patient, her physical condition, the feasibility of performing some more conservative procedure, and finally, but not of least importance, on the consent of the patient herself after all aspects of the operation have been explained to her. The operation is also indicated in the treatment of prolapse of the vagina or vaginal hernia after hysterectomy,

either of the abdominal or vaginal type, recurrences after the interposition operation, and in the treatment of prolapse in nulliparous women.

Subtotal colectomy, or the LeFort operation, was devised for the treatment of prolapse by vaginal occlusion without removal of the uterus. It provides for the drainage of the secretions of the uterus and cervix by the formation of a transverse cavity beneath the cervix, which communicates at each end with two laterally placed canals leading to the surface at the vaginal orifice. Such provision for permanent drainage is essential in all cases in which the uterus is left in place, even after the menopause. In the LeFort operation two rectangular areas, one on the anterior and one directly opposite on the posterior wall of the vagina, are completely denuded of mucosa. The upper limit of each rectangle should not extend beyond a point 2 cm. below the cervix; the lower limit posteriorly corresponds to the mucocutaneous junction; anteriorly it extends nearly to the urethral opening. The width of each rectangle should be such that the mucosa remaining on each side will form a canal about 1 cm. in diameter. After bleeding is controlled the denuded rectangles are then accurately apposed and sutured together from above downward with interrupted catgut stitches. A perineal repair when indicated should be performed as part of the operation. The experience of Adair and DaSef¹ with this operation has been very satisfactory, especially since 64% of the patients on whom they performed it had some condition contraindicating extensive operative procedure. They emphasize that the prolapse should be capable of reduction, erosions of the cervix and vaginitis should be eliminated by suitable treatment, the corpus and adnexa should be free from disease, the sexual life of the patient should no longer be of importance and the consent of the husband should be obtained. In reviewing the literature they collected 260 cases with satisfactory results in 86%. In those cases in which there were recurrences the causes were almost always the same, either failure to make the lateral channels small enough to prevent recurrence of the prolapse through the side canals, or failure of the sutures to hold, with resulting partial separation of approximated surfaces. Deaths have usually been due to thrombosis and cardiovascular disease. There is one major objection to the operation and that is that it prevents any later examination of the cervix. For this reason it is necessary that the cervix and the uterus should present no abnormality at the time of operation and if any suspicious lesion is present, a vaginal hysterectomy should be done. However, the incidence of uterine carcinoma in women with atrophied uteri is not great and they have found only one report of carcinoma following the operation. In order to overcome the necessary termination of sex life which the classical LeFort operation entails, and interesting modification has been devised by Goodall and Power² in which the denudations of the vaginal walls are made in the shape of triangles in the upper part of the vagina, the apices of the triangles pointing toward the vaginal outlet. The denudation usually involves only the upper third of the vagina so that when they are apposed there remains a single vagina in the lower two-thirds with a double vagina in the upper part. The apposition of the upper anterior and posterior vaginal walls prevents prolapse while the single vagina below permits sexual intercourse.

At the Mayo Clinic, according to Masson and Knepper,¹² both partial and complete colpsectomy are used with very satisfactory results, the average age of the patients being 58.5 years. The exposure and irritation of the vaginal mucous membrane had caused an unnatural dryness and thickening which usually had caused the cessation of sexual relations before the patients sought medical advice. In performing complete colpsectomy, after removal of the uterus by vaginal hysterectomy, the broad ligaments are approximated in the median line and firmly fixed well up under the pubic arch. They are then sutured posteriorly to the levator ani muscles which have been thoroughly freed and sutured in the median line as in an ordinary perineorrhaphy. In this manner a strong pelvic floor is reconstructed and the closure of the rest of the vagina is easily accomplished, after removal of all mucous membrane, by interrupted transverse sutures, some of which are silkworm gut, and are left in place for 12 to 14 days. It is advisable to provide for drainage by inserting a small tube. If an enterocele is present the peritoneal sac should be removed before commencing the closure.

Prolapse After Hysterectomy. The occurrence of prolapse of the vaginal walls some time after the performance of a hysterectomy is a most unpleasant sequel. While in many instances it can probably be corrected by a colpocleisis as previously described, if it occurs in a sexually active woman, some other method of treatment must be considered. Brady⁴ has met this difficult situation in 1 instance by making a lower midline abdominal incision and opening the fascia and peritoneum only in the upper part of this incision. A Cameron light introduced into the vagina pushes the vaginal vault upward so that it is easily recognized from within the abdomen. Three medium-sized braided silk sutures are introduced from above into the top of the vaginal vault and are then passed through the peritoneum and fascia of the lower part of the wound and tied on the external aspect of the fascia, thus fixing the vagina to the anterior abdominal wall. The relaxed round ligaments were reefed and sutured to the vagina, preventing the bladder from prolapsing laterally. A perineorrhaphy completed the operation.

Ward²⁰ successfully treated a case of this type, the patient having been followed for 4 years after operation. The operation he employed consisted of a reconstruction of the round ligaments of the uterus by the use of preserved ox fascia lata. After suturing the fascia lata to the vault of the vagina from within the abdomen, these newly made ligaments were continued anteriorly under the peritoneum of the bladder to give added support to that organ. The new round ligaments were entirely extraperitoneal so that there was no danger of intestinal obstruction from free bands within the peritoneal cavity.

Intestinal Obstruction Complicating Prolapse. Although prolapse is often complicated by an enterocele, incarceration and obstruction of the contained bowel is rare. The case reported by Frank^{7b} was a 42-year-old multipara who had had a reducible prolapse for 1 year. Two weeks before admission the prolapse became irreducible and for 2 days no flatus was expelled. On admission she presented a huge prolapse ulcerated in several places, which could not be reduced after

considerable trial. On opening the abdomen it was noted that the prolapse contained both large and small bowel which could not be reduced. After decompression of the small bowel by needle puncture, the bowel could be replaced into the abdominal cavity and then after considerable pressure from below the large prolapse was inverted and the abdomen closed. Four laparotomy pads were packed into the vagina to prevent recurrence of the prolapse. The patient had a rather stormy convalescence due to various complications but 8 weeks later it was possible to perform a parametrial fixation for the cure of the prolapse with a successful result when seen after 14 months. One of the reasons that irreducibility of prolapse is rarely encountered, according to Frank, is that unless an extremely sluggish and unintelligent patient suffers from this trouble, the symptoms are so acute and violent that immediate help is sought. In the early stages before stasis and edema have occurred, reduction should always be possible.

Intestinal obstruction following round ligament operations has been recognized as a possibility for many years, but since it rarely occurs we are prone to think lightly of it. A personal experience with 2 cases within 1 year has vividly brought to my mind the seriousness of this complication. C. C. Norris has also seen 2 cases and a third case following shortening of the uterosacral ligaments. These cases, which were reported by Michael¹⁴ were both instances in which the small bowel became strangulated between the anterior abdominal wall and the round ligament which had been sutured to it, leaving a lateral pocket. It is important that such a condition should be strongly considered in any patient who presents symptoms of ileus following a previous uterine suspension. Since this experience, it has been our practice to close the space between the round ligament and the abdominal wall on each side in all cases in which the Olshausen type of operation is done, feeling that the slight additional operating time is well spent. That such obstructions do not only occur after this type of operation is shown by the report of Arnold.² In his case a loop of ileum became obstructed through the broad ligament at the site where the round ligament was pulled through in the performance of a Baldy-Webster operation 9 years previously.

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DERMATOLOGY AND SYPHILOLOGY.

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LYMPHOGRANULOMA VENEREUM.

LYMPHOGRANULOMA venereum is especially deserving of consideration as an excellent example of both the speed and the completeness with which modern investigative methods can organize from scattered beginnings the completely evaluated picture of a disease entity. Within a quarter century, climatic bubo or so-called suppurative inguinal adenitis of unknown etiology in males (Trousseau,¹²¹ 1865; Godding,²⁸ 1896); Nicolas-Favre's disease,¹⁸ subacute localized and suppurative lymphogranulomatosis in the inguinal region, and the lymphogranuloma inguinale of the years immediately preceding the World War, have all been swept into one category of what appears to be a disease entity. The venereal origin, although suspected for many years, was finally proven by Phylactos⁸⁵ in 1922. Gamna,²⁵ in 1923, had reproduced the inguinal lymphatic form in guinea-pigs. The successful transmission (1930) of the infection to other animals by Hellerström and Wassén⁴⁴ with confirmation by Levaditi and his coworkers^{62, 63a, b, c, 64, 65} (mouse-brain inoculation) and by Findlay^{21a} established experimentally the etiologic unity of the disease. Frei's introduction from Jadassohn's Clinic, in 1925,^{23a, 24} of the intracutaneous test made possible the inclusion of esthiomène and poradenitis and finally of rectal stricture (Jersild^{50a, b}) with the clinical and pathologic picture of lymphogranuloma venereum. From the literature between 1930 and 1936, it is now possible to collect (Bacon^{3b}) 3977 reported cases which conform to the newer conception of the disease entity, even though it is not wise as yet to speak of them all as absolutely proved. This rapidly developing knowledge has inevitably resulted in a confusion of nomenclature for which no immediate resolution, unless by international agreement, seems in sight. The name for the disease officially adopted by the American Medical Association is "lymphogranuloma venereum." Among the chief summaries of the subject in the literature are those by Hellerström,⁴³ DeWolf and Van Cleve,¹⁷ Sulzberger and Wise,¹¹⁴ Wolf and Sulzberger,¹²⁶ Cole,¹¹ Stannus,^{112a, b} Martin and Bacon,⁷³ J. C. Levaditi⁶⁷ (experimental), Thompson,¹¹⁹ Löhe and Schlossberger⁷⁰ (complete clini-

cal and experimental), Bloom,^{7b} W. Frei,^{23c} and Jones and Rome.⁵¹ The chief workers and active study centers of the world include Hellerström (Stockholm), Levaditi (Paris), Findlay (London), Stannus (London), Miyagawa (Tokyo). Wilhelm Frei who originated the cutaneous test while in Breslau is now an expatriate, working in New York City (Montefiore Hospital). Nicolas and Favre (Lyons, France) are still active in the field. The work of European investigators was introduced to this country by Sulzberger (New York), and popularized by Cole (Cleveland). Grace and Suskind^{32,33a,b,c,d} have worked actively with mouse brain antigen. Strauss and Howard^{46,113a,b,c} have written extensively on the Frei test; extended American work on anorectal granuloma has been done by Martin⁷² and Bacon⁷³ (Philadelphia), Colé¹¹, Mathewson⁷⁴ and Bloom.^{7a} Some of the most important recent investigative work, particularly on the culture of the virus, is that of Tamura^{115a,b} (Cincinnati). W. E. Coutts (Santiago, Chile) has been the chief South American student.

Work on the Virus. The priority and validity of the earliest work on the virus, including that of Gamna (1923) and Favre (1924) is discounted by Findlay, who credits Gay-Prieto²⁶ with the earliest recognition of small cytoplasmic granules in the cells of the inguinal bubo, as also described by Findlay^{21a} in 1933. The work of Miyagawa and his group^{78a,b} seems supportive of the contention that these granules actually represent the infective agent. They are uniformly present in the lesions of lymphogranuloma venereum in man, in the brains of infected mice and monkeys, and in the experimental buboes of guinea-pigs. The presence of similar granules in the chorio-allantoic membrane of the developing chick embryo infected with lymphogranuloma venereum and in the cells of the rabbit's cornea grown in tissue culture is also regarded as confirmatory. Tamura^{115a,b} has demonstrated the presence of granules in the tissue containing Maitland-Tyrode medium cultures of the virus. The dimensions of the virus as measured by various observers are similar to those of the vaccinia virus, $0.24\ \mu$ to $0.33\ \mu$ in diameter, easily passing through such filters as Chamberland L₂ and L₃ Berkefeld and Seitz.^{78a} An antiserum prepared in rabbits, from which the elementary corpuscles have been removed by differential centrifugation contains no viricidal immune bodies, while an antiserum prepared from relatively concentrated suspensions of elementary bodies does contain viricidal immune bodies (Findlay^{21b}). Tasaki,^{116a} Grace and Suskind,^{33d} Coles,¹² Herzberg and Koblmüller⁴⁵ have all confirmed the virus work of the Japanese investigators. Landmarks in work on the virus have included Levaditi's transmission of the infection to the mouse brain,⁶⁴ the demonstration of the virus in the pus of the inguinal bubo (Hellerström and Wassén,⁴⁴ Cohn and Kleeberg¹⁰ and others) and the demonstration by many workers of the presence of the virus in all the recognized lesions of the disease (hypertrophic and stenotic inflammatory rectal lesions,^{90,120} vulvar esthiomènes^{55a,b} and primary genital lesions⁷¹). Beginning with the transmission of the infection to monkeys by Hellerström and Wassén,⁴⁴ the infectibility of many animals and especially of rodents has been demonstrated. The horse, rat, chicken and frog have thus far proved refractory.⁶⁷ In the monkey, the virus does not remain localized in the nervous tissues, but passes the blood-nervous tissue barrier and is carried by the lymph and

leukocytes to regions of the body rich in histiocytic cells. In the guinea-pig, the infection seems limited to the local primary lesion and its regional lymph nodes.

In addition to the demonstration of the virus from all recognized lesions of the disease, it has been shown to be present in the spinal fluid by von Haam, and R. D'Aunoy³⁸ and in the secretions of a case of acute conjunctivitis.⁶⁰ Of even more significance is the statement of P. Ravaut,⁶⁷ that the virus was obtainable from the intact vaginal mucous membrane of a patient with enlarged inguinal lymph nodes, and that of Caminopetros,⁸ who purports to have found the virus present in the vagina at least 18 months after infection. It has also been identified in non-bacterial urethral and vaginal discharges. There seems reason to believe (von Haam and D'Aunoy) that the virus of the disease exists in human beings as long as the lesions are present.

Löhe and Schlossberger's⁷⁰ valuable review demonstrates clearly the shortcomings of our immunologic knowledge concerning the infective agent. They find that successive animal passage heightens virulence, but as yet, nothing in the way of vaccination experiments with attenuated virus or any immunizing prophylaxis seems to have developed. Suggestions of tropism and elective localization include the observations on migration of the virus to centers of histiocytic activity above mentioned and the clinically recognized predilection for the localization and extent of the process in the lymphatic system. This lymphotropism, in fact, is responsible for the important differentiations in types of involvement observed in clinical practice.

Epidemiology. Lymphogranuloma venereum, so far as present knowledge indicates, is distinctly a venereal disease. Non-venereal and extragenital infections have thus far been reported almost entirely among physicians, research workers, nurses, and children accidentally inoculated by such conveyors of the virus as enema tips. H. Levy's report⁶⁸ disclosed only 9 cases in children throughout the entire literature, and an additional one reported by the author (see also Elitzak and Kornblith²⁰). A characteristic early transitory vaginal discharge with urethritis in children accompanied by inguinal adenitis was the chief suspicion-arousing characteristic. Nicolau⁸² believes the transmission to the child in his case was by way of the bed-clothing. Finger inoculations have occurred in workers with the disease, with lymphatic extension *via* the axilla. Tongue and tonsillar primary and secondary lesions have been recorded, usually ascribed to perversion. Löhe and Schlossberger⁷⁰ cite Walter as having described a case and themselves report an instance in which they believe evidence of congenital transmission of the disease is disclosed. Studies in epidemiology must take into account the fact that the virus is active at room temperature for 24 to 48 hours, loses its virulence at a temperature of 46° C. for 30 minutes, is killed in 10 minutes at 56°, but is unaffected by freezing temperatures for 1 day. It remains active after drying for 30 days, and may transmit the disease in dilutions as great as 1 to 10,000.^{78b} The extremely important question of asymptomatic carriers of the disease deserves further study. The identification in routine testing of persons who have positive Frei tests with no history of lesions for years; the occurrence of an infective urethritis with no other manifestations, and of an apparently normal condition of the vaginal mucosa accompanied

by the presence of the virus, suggest the public health importance of this group of phenomena.

Most of the evidence that has been collected relative to the distribution of the disease through the population has been based on studies of clinic patients and upon those who are sexually promiscuous or actually engaged in prostitution. Whether the figures available therefore represent sound conclusions on the distribution of the disease throughout the population and in medical practice may well be doubted. Gray, Hunt, Wheeler and Blache³⁴ studied the prevalence of the disease in St. Louis, and found the number of positive Frei tests in whites to be 3.4 %; in colored patients, 40 %; white prostitutes were positive in 4.4 %; colored prostitutes in 47.7 % of cases. Not more than 40 % of the cases identified were active. De Wolf and Van Cleve, reporting from Cleveland, found 58 positive Frei reactions among 1010 persons treated. Haim and Mathewson,⁴⁰ studying the incidence in San Francisco (1937) found 60 proved cases on the records of the Marine Hospital; 46 proved cases were observed in the San Francisco General Hospital. Seven hundred adults were surveyed by means of Frei test, with 2.7 % positive and 2.7 % doubtful in the San Francisco General Hospital and 8.9 % positive, 3.2 % doubtful in the Marine Hospital. Of the latter group, one-third were venereal disease cases. Tasaki and Kamimura,¹¹⁷ examining prostitutes in Harbin and Mukden (995 cases in all) found 12.8 % of the Japanese, 23.4 % of the Koreans, and 27.2 % of the Chinese prostitutes with positive Frei tests. Those without clinical signs constituted approximately 80 % of the group. Goldblatt³⁰ found that 32 % of the prisoners quarantined for venereal diseases in the Cincinnati workhouse gave positive Frei tests when tested with several antigens. Clyne,⁹ at Fort Sam Houston, Texas, during a 13 months' period, recognized 48 cases of lymphogranuloma venereum, and, comparing the incidence rate with that of other venereal diseases, found that it constituted 4.1 % of admissions (that is, 48 cases in 1158 of syphilis, gonorrhea, chancroid and lymphogranuloma venereum). This is approximately one-fourth the incidence of chancroid. Simon and Bralez¹¹¹ (Saint-Lazare Hospital), in 412 entries of unsuspected individuals on a hospital service, found lymphogranuloma venereum as judged by the Frei test, in 4.1 % of cases. Hanschell,⁴¹ at the Seamen's Hospital, London, found 130 cases among 17,900 admissions for other genito-infectious diseases. The comparative rarity of the disease in Great Britain has been mentioned by Stannus.^{112a}

An examination of the available reported material tends to indicate that neither sex nor race influences the incidence or distribution of the disease. It appeared that the asserted greater prevalence of the infection in the negro is more probably due to sexual promiscuity and high rate of exposure than to any intrinsic susceptibility on the part of the negro individual. So far as age incidence is concerned, the statistics collected by Hashimoto and others⁴² tend to indicate that the peak of incidence corresponds to the peak of sexual activity, and contains no element of age, immunity or predisposition (see also A. S  zary and others¹⁰⁷).

The geographic distribution of the disease has shown variations, dependent on the source of the material, more obviously than any other consideration. It is obviously no longer to be regarded as a seaport

disease, and the distribution of the some 4000 reported cases indicates that interest and location in a region where sexual exposure runs high in the population gives an impression of prevalence. Nonetheless, an observer of Frei's experience has stated that the disease appears to have endemic centers at times of maximum prevalence which do not necessarily conform to those of other venereal infections. Epidemic and endemic foci are occasionally dependent on single sources of infection, as in the case of the Greek island reported by Serefis,⁹⁶ in which practically the entire population was affected, following the introduction of the disease by a single infected prostitute.

Public Health Considerations. Frei^{23c} summarizes the situation with reference to public health control (1938) by a comparison with syphilis, in which he points out that only one laboratory diagnostic method of lymphogranuloma venereum exists as compared with two for syphilis, and that the supply of diagnostic material is thus far limited though improvable with the development of new methods (including possibly mouse-brain antigen). No method of treatment of lymphogranuloma venereum thus far proposed has the immediate disinfectant action of the arsenicals in syphilis. So far as we have been able to ascertain from the available literature, no provisions are contained in the laws of the states in this country relative to reporting, and the availability of antigen for diagnosis is practically entirely that of private sources of supply. Sweden, in 1934, was the first country to take national cognizance of the disease as a public health problem, though the Office International d'Hygiene Publique⁸³ has thus far made no recommendations, but has conducted an international investigation. As in the case of syphilis, it should be pointed out that the woman is apparently the uncontrollable and in many respects the most important part of the reservoir of infection. Since vaginal secretions can be infectious apparently in the absence of any open lesion,^{8,67} and since the inoculative stages in the woman usually involve the posterior lip of the cervix and the deeper portions of the posterior wall of the vagina, it is obvious that clinical detection of the disease in this sex, especially will lag far behind its public health desirability. Routine Frei test examination of prostitutes has the serious defect that positive tests are obtained in persons in whom the disease has definitely reached the inactive and presumably non-transmissible stage.

Since the disease is more definitely a genital infection than syphilis and the area of infection more distinctly confined to the mucosal surfaces, it would seem that mechanical prophylaxis, if effectively carried out, is probably as useful in prevention as anything at present available.

The Clinical Picture. It is not the purpose of this review to detail the clinical course of lymphogranuloma venereum, but the following statement briefly summarizes the essential facts. A primary sore or lesion usually appears from 2 to 5 days after the infective coitus and in the male is most commonly observed on the coronal sulcus, but may appear on the glans, the prepuce, or in the urethra. There may also be a balanitis. In females, while the inoculatory lesion may occur on any part of the external genitalia, the usual site, as already mentioned, is the posterior vaginal wall, posterior lip of the cervix, or in the neighborhood of the fourchette. The lesion is a small herpetiform vesicle or ulcer, circular or lenticular, sometimes multiple, with clean-

cut edges surrounded by a reddened zone but with no induration or infiltration. The base of the ulcer is whitish gray and forms a small rounded hollow of pin-head size. The lesion is asymptomatic, heals spontaneously and is often missed both by the patient and physician. Hashimoto and others⁴² found the primary lesion to consist of a small erosion in 56 %, an infiltrated papule in 39 %, and a herpetic lesion in 5 %. The incubation period in their series, it should be noted, can be as long as 5 weeks (3.8 %) but was 1 week or less in 70 % (see also S  zary and Friedmann¹⁰³). The lymphotropism of the virus leads to the development of a bubo in the drainage area of the primary lesion, the incubation period for this manifestation from the time of infection ranging from 4 days to more than a hundred, and being most frequently 10 to 29 days (48 %). The early impression that lymphogranuloma venereum was exclusively a disease of males, as well as the failure to identify the vulvar and anorectal granulomas with lymphogranuloma venereum was a consequence of the lymphatic distribution of the virus. When the primary lesion occurs in the inguinal lymphatic drainage area, whether in male or female, inguinal buboes and esthiom  ne are the prevailing manifestations. When inoculation occurs in the vagina or upon the cervix, direct extension of the infection through the recto-vaginal septum leads to the syndrome of anorectal lymphogranuloma. The bubo localization is prevailingly inguinal and iliac (more frequently the latter) and more frequently unilateral than bilateral (Kitchevatz and Alcalay.⁵⁴ Occasional inguinal, femoral, and inguino-femoral and iliac involvements occur. Hashimoto and others⁴² found the inguino-iliac and inguino-iliac-femoral to represent 58.4 %, the inguinal 36.4 %, and the inguino-femoral 5.2 % of the localizations. From the secondary adenopathy at first recognized by the patient through a sensation of stiffness and aching followed by swelling, the process may come to an end, or after retrogression, may light up again. It usually extends, however, until all the glands of the group are usually involved, with considerable periadenitis, the mass becoming fixed and adherent to the skin which is of a rather characteristic purplish color (Stannus^{112b}). The iliac glands may form masses as large as a child's head. Inflammatory changes continue with softening, and the formation of abscesses and fistul   from which a characteristically thick viscid, tenacious opalescent yellowish-white pus exudes and in which no organisms can be demonstrated by the usual cultural methods. In a period usually extending from 2 months to 2 years, the glandular swelling subsides, drainage is complete and healing takes place. If the destruction of glands and surrounding tissue is widespread, secondary elephantiasis of the leg and pudenda may follow, or there may be a complicating phlebitis. Extensive and critical suppuration of the lumbar glands, extensive destruction of the psoas muscle and extension of the infection to articular surfaces and to the kidney and adrenals of the involved side have all been observed.

The constitutional symptomatology, while not highly specific, adds lymphogranuloma venereum to the group of conditions to be considered in persons who present slight fever,^{56,102} slight leukocytosis with mononucleosis,^{9,48,57a} increased sedimentation rate,^{57b,124} and alterations in blood lipids and proteins.^{36,91,116,124,125} This last-mentioned change is regarded as of diagnostic significance by Jersild,⁴⁹ Howard, Eisenman

and Strauss.⁴⁷ After summarizing the observations of a number of investigators and their own work, Rosen, Rosenfeld, Bloom and Krasnow⁹² support the diagnostic importance of the lipid-globulin relationship by observations on 116 cases. Hyperglobulinemia occurred in 100% of their cases, and was most marked in the late stage (rectal stricture and esthiomène). They rate this hyperglobulinemia then as a valuable diagnostic lead. The serum lipids were uniformly decreased. In chancroid, for example, there may be an increased globulin content but there is no decrease in the lipids. These observers found that treatment of the lymphogranuloma venereum brought the lipid values to normal but left the globulin unchanged. Gutman and Wise,³⁷ reporting on the positive formolgel reaction associated with hyperglobulinemia in lymphogranuloma venereum, point out that the hyperglobulinemia may be responsible for other somewhat erratic or abnormal findings in the blood of patients with this disease. For example, the high sedimentation rate, often greatly in excess of the level consistent with the degree of obviously active infection; the falsely positive and repeatedly anticomplementary Wassermann reactions reported in the literature,¹¹⁴ may be regarded as phenomena attendant upon the hyperglobulinemia.

That lymphogranuloma venereum is a systemic infection, is borne out by the occasional examples of meningitic and meningo-encephalitic involvement.¹⁵ Rajam,⁸⁹ in reporting a fatal case, summarizes the spinal fluid findings in the reported examples, including Midana and Vercellino's examination⁷⁷ of 11 cases, in which all except 2 were normal. The abnormalities reported by this author and by Kitagawa⁵³ are apparently not specific or characteristic (see also Clyne,⁹ Mollaret and Vieuchange⁷⁹). It will be recalled, however, that the virus has been recovered from the spinal fluid.³⁸

Jones and Rome⁵¹ have collected the literature of systemic manifestations, including pulmonary involvement and ocular localizations with regional adenopathy, tonsillar ulcers, ulcerative angina, arthritis at points distant from the site of initial involvement, occasionally simulating rheumatic fever or purulent arthritis. The dermatologic manifestations include erythema multiforme, erythema nodosum, scarlatiniform eruptions, papular lesions, ulcers, and giant keloid formation. Particular interest attaches to the characteristic lymphogranulomatids reported by Saenz⁹⁴ and by Goldberg and Fondé²⁹ which are indicative, theoretically at least of vascular dissemination and allergic characteristics in the disease.

The "late" lesions of lymphogranuloma venereum are unfortunately seen in the large majority of cases only after extensive scarring has taken place, and are, therefore, to a considerable degree, residua rather than active and treatable infectious lesions. The relatively unsatisfactory drainage of the anorectal type of infection, according to Stanus^{112b} prevents rapid evacuation of the virus from the infected locality and leads to the extensive destructive and deforming lesions of esthiomène and anorectal lymphogranuloma.⁹³ Rosser, in whose opinion Collier Martin concurs,⁷² pointed out the importance of the keloid or fibroplastic diathesis in the negro in producing the extraordinary hypertrophic and elephantiasic pictures, particularly in the negro female, to which the latter author once applied the term "negromata." Finkel-

stein²² and Stannus^{112b} and others have all directed attention to the low position of the strictures in anorectal granuloma, characteristically recognized in the Roentgen ray at 2 and 6 cm. above the anal orifice. Finkelstein also calls attention to the roentgenologic picture of the tubular arrangement of the lesion with indistensible walls and preservation of the mucosal pattern, and perirectal sinus visualization. The special student of the rectal pathology and clinical manifestations should read the papers by Cole,¹¹ by Vander Veer, Cormia and Ullery,¹²² by Mathewson,⁷⁴ by Bloom,^{7a} and by Bensaude and Lambling,⁵ and Stannus.¹¹²

The Frei Test and Other Diagnostic Procedures. Inasmuch as the Frei cutaneous test is the principal diagnostic resort at the present time, the only procedure which is applicable to surveys and routine testing and the most important diagnostic or confirmatory evidence available in the early stages of the disease, some description of special technical detail is worthwhile. Two main sources of antigen, so-called, are recognized: the pus from the inguinal bubo and emulsion of the brains of intracerebrally infected mice. With reference to the Frei antigen, the most recent specifications of the author^{23c} of the test may be quoted:

"The material needed consists of the diluted and sterilized pus of proved, non-ruptured pure buboes of venereal lymphogranuloma. One-tenth cubic centimeter is injected intracutaneously and the reaction is read after two days. In a positive case, one finds an inflammatory papule of at least 0.5 cm. in diameter, often with peripheral erythema and sometimes with a central pustule. In negative cases there is none, or very little reaction after two days. Only tested vaccines corresponding to these conditions should be available for general use. On account of the possibility of generalized or focal reactions, it is not advisable to make the test in hyperacute stages of the disease or in cases in which suppuration occurs near the peritoneum."

A positive reaction does not prove that the disease still exists, because the power to react to the test remains in healed cases for decades. A negative reaction in cases of venereal lymphogranuloma occurs in the earliest stage of the bubo, and in some cases in which there is transitory or constant anergy. In cases of anergy a positive result may be obtained by the so-called inverted test, in which the patient's sterilized pus is injected into the skin of a patient with proved lymphogranuloma venereum, producing a positive reaction, or the usual vaccine is injected intravenously instead of intracutaneously into the suspect, and if he has the disease, he may respond by a generalized febrile reaction. It may be said that the venereal lymphogranuloma cutaneous test results in about 95% of positive reactions when buboes have developed, and in about 90% when there is ulcerative elephantiasis. In discussing the sources of error in the use of his test, Frei^{23b} has given unspecific inflammatory reaction resulting from the use of vaccines contaminated with living or dead bacteria as the chief source of trouble. "The danger of contamination is very great since the vaccine is prepared without any antiseptic and thus furnishes an excellent culture medium. For purposes of sterility one must therefore watch and control every little step in obtaining, preparing and using the vaccine. For example, I (Frei)

originally put the vaccine up in small vials and used them on several occasions. Later, to assure sterility, I replaced the vials by small ampoules, each containing sufficient vaccine for only one test. Here in America, I found in various places the old vial system, but with one difference; namely, that the vaccine is aspirated through the stopper, while I had to remove the stopper."

In a bacteriologic study of material prepared and supplied with rubber stoppers, Frei reached the conclusion that the use of a rubber stopper is a potentially fertile source of trouble from infection of the vaccine, especially where the general practitioner repeatedly punctures the cap under merely alcohol sterilization. In discussing the inverted test especially, when a similar technique is applied to other body fluids and discharges such as mucoid urethral secretions, spinal fluid, bowel secretion from ulcerative colitis^{84a,b} and so forth, Frei believed that serious non-specific elements may enter into the interpretation. Sézary and Georges-Lévy¹⁰⁴ found most of the difficulties due to defective antigen, and Durel and Dreyfus¹⁹ believe the quantity ordinarily used to be insufficient. They insist on 0.3 cc. as the optimum amount.

Frei has thus far refused to express himself on the use of mouse-brain antigen, on the ground of lack of experience. A controversy over the specificity of mouse-brain antigen has, however, developed among various observers, which is discussed by Grace³¹ in recent correspondence. Grace insists upon the importance of the measurement of the papule produced by the antigen as the only reliable means of differentiating between non-specific reaction due to injected foreign tissue substance and reaction actually due to the presence of the virus. He states that mouse-brain antigen has been so standardized that 0.1 cc. intradermally in lymphogranulomatous subjects produces an erythematous papule not less than 7 mm. in diameter and usually from 7 to 10 mm. In 823 control tests, no papule larger than 6 mm. was produced, and in less than 6% only were the papules as large as 6 mm. The necessity for this type of accurate measurement of the papule size and the differentiation between specific and non-specific reactions based on such comparatively small differences has led Binkley and his associates⁶ to believe that the test as performed with mouse-brain antigen is unreliable (see also Strauss and Howard¹³⁶). Favorable reports, however, have been published by von Haam and Hartwell,³⁹ Lichenstein and von Haam,⁶⁹ D'Aunoy and von Haam,¹⁴ Bacon,^{3a} and Bloom.⁷⁶

Melzer and Sipos⁷⁵ have experimented with a complement fixation test for lymphogranuloma venereum with 87.5% positive and 12.5% non-specific reactions. Midana,⁷⁶ on the other hand, was unable to obtain any positive complement fixation tests on 21 patients with lymphogranuloma venereum. Coutts and Ponce¹³ have reported a method which gave 100 negative controls in the presence of highly syphilitic sera, and believe the method therefore to be highly specific for lymphogranuloma venereum. The blood serum changes which may be explanatory of anticomplementary and falsely positive blood Wassermann tests for syphilis in patients with lymphogranuloma venereum have been mentioned above.

Pund, Greenblatt and Huie⁸⁷ have discussed the usefulness of biopsy in the diagnosis of lymphogranuloma venereum from tissue. The histologic picture for those who desire to study this question has been

described by a number of authors, including Stannus,^{112a} Thompson,¹¹⁹ De Wolf and Van Cleve,¹⁷ and Jones and Rome.⁵¹ Frei believes that the microscopic study of sections offers some useful points in differentiation, of lymphogranuloma from other inflammatory and suppurative diseases, including tuberculosis.

Culture of the virus is still a purely laboratory method not yet available for diagnosis. Animal inoculation, however, has a limited value, especially the inoculation of mice, which develop an encephalitis following intracranial injection. This presents fairly characteristic histologic pictures, from which the virus may subsequently be obtained for test purposes.

Treatment of Lymphogranuloma Venereum. Any discussion of the relatively unsatisfactory treatment of this disease should be preceded by emphasis on the occurrence of spontaneous recovery. Its frequency is inferred from the large number of Frei test positives obtained in surveys in patients who no longer show any active clinical evidence of the disease. The treatment of the early manifestations of lymphogranuloma venereum includes local surgery and irradiation. Stannus^{112b} states that in early cases of inguinal adenitis with only one or two glands involved, a minimum of periadenitis and the skin free, radical excision is often effective. On the other hand, any attempt to remove a large mass of matted glands and adherent tissue must be deprecated. Aseptic aspiration, repeated when necessary, as long as the skin is intact, is probably the wisest course. Negru⁸⁰ found that in non-purulent cases, Roentgen irradiation with massive doses of hard rays produced healing in at least 50 % of the cases. In draining or granulating cases, irradiation is also useful, and promotes healing of the operative wound.

The drug therapy of lymphogranuloma venereum testifies by the multiplicity of remedies to non-specific and relatively unsatisfactory results. Local injections, as of glycerin, or xylol-iodoform, have little value. Iodine and iodide (Lugol's solution), 10 cc. in an equal quantity of saline, daily intravenously, or 10 cc. of a 10 % solution of sodium iodide have been favorably reported. Copper ammonium sulphate, Solganal (a gold preparation), sodium salicylate intravenously, and by mouth, fever therapy, and non-specific vaccine and non-specific protein all have some good results to their credit. The most important drug in the treatment of the disease at present is unquestionably antimony, which, as potassium antimony tartrate, has probably had the most extended trial.⁹⁵ Lithium antimony thiomalate (anthiomaline) seems to have had the most favorable reports. Sézary and his associates,^{98-101,106} Setien and Farinas,⁹⁷ Shaffer, Fondé and Goldberg¹⁰⁸ and others^{1,81} have emphasized the striking symptomatic effects of this antimony compound and its relative freedom from toxic effects. All writers are said to report that 50 or 60 % of cases show rapid improvement, 20 to 25 % show a slow but good effect, and 20 to 25 % remain unresponsive. It is notable that considerable relief can be obtained even in the anorectal syndrome. Sézary,^{98-101,106} however, failed to note much benefit in such cases in which, of course, the proportion of scar to active process must be an important consideration. The drug is administered 2 or 3 times a week with an initial dose of 0.06 gm. and increments of 0.03 gm. until the rheumatoid pains typical of anti-

mony reaction appear. The dosage is then reduced until the pains are barely perceptible several hours following the injection. This dose is usually approximately 0.12 to 0.24 gm., but some patients may tolerate as much as 0.3 gm. A course totals 2 to 4 gm. of the drug (12 to 20 injections) with rest periods of 2 to 3 weeks before beginning the second or final course. Fuadin, another antimony preparation, is rated an effective drug by a number of observers, and definitely to be preferred to surgery as a means of shortening the course in most cases.

Shaffer and Arnold¹⁰⁹ treated 22 patients with lymphogranuloma venereum by the use of sulphanilamide, with 4 seemingly complete recoveries, 11 marked improvements. Their study of the German and French literature^{50,66} confirms this favorable experience (see also Qualls⁸⁸). Gjurić²⁷ obtained his best results with fuadin and prontosil (see also Bär⁴). Shropshear¹¹⁰ had excellent results in the ano-rectal syndrome.

The biological treatment of lymphogranuloma venereum includes first of all the use of the Frei antigen ("vaccine") derived both from human and monkey^{16,61} and from mouse-brain sources, and administered both intradermally and intravenously. Wien and Perlstein¹²³ have reported on 200 patients in a series of 500 treated by this method with the conclusion that conservative treatment by the intradermal injection of Frei antigen is more effective and less associated with destruction and disability than any other procedure. Prehn⁸⁶ gives a series of at least 8 injections, 1 every other day intradermally, close to the site of the lymphadenitis with very favorable effects. Anderson and Harnos² treated 48 cases with sterile potent Frei antigen, diluted 4 times (1 to 4 or 1 to 28 dilution of the heat-treated pus in physiologic salt solution) which was effective in doses ranging from 0.05 cc. to 1 cc., treatment being continued until the sinuses had healed and the adenopathy subsided. Six to 12 doses were usually necessary. The antigen has also been given intravenously by several observers, the most recent report being that of de Gregorio³⁵ who treated 50 patients with more rapid results, following 12 to 14 injections, than by any other method.

Convalescent serum was employed by Katz and Sagher⁵² with favorable results, but there have been no further reports of this method apparently. Thomas and McCarthy¹¹⁸ employed a bouillon filtrate of hemolytic streptococcus and other organisms obtained from the wound in 1 case, with healing in 2 months. The uncertain interpretation of such results in view of spontaneous cure is obvious. Chaulmoogra oil was used by Landrock⁵⁸ without results. The surgery of the hypertrophic and elephantiasic manifestations and the management of rectal stricture is a special field in which results are largely dependent on skill and experience, for the tissue in most cases heals satisfactorily. It must be borne in mind that all the forms of treatment previously discussed are asserted to exercise some beneficial influence and are asserted to improve the outlook both objectively and symptomatically. Surgery should therefore be a secondary rather than a primary resort in present-day practice.

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PHYSIOLOGY.

PROCEEDINGS OF
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The Effect of Progressive Sympathectomy on the Hypertension Produced by Increased Intracranial Pressure. NORMAN E. FREEMAN and WILLIAM A. JEFFERS (Harrison Department of Surgical Research and the Robinette Foundation, University of Pennsylvania). The intracranial pressure was raised, in dogs anesthetized by nembutal, by intracisternal injection of sterile physiologic salt solution at 200 mm. Hg. pressure. The blood pressure was recorded from the femoral artery by means of a Hamilton manometer. In normal dogs, the systolic pressure increased to over 300 mm. Hg. and the diastolic increased from 120 to 180 when the cisternal pressure was raised to 200 mm. Hg. The dogs were then allowed to recover before being subjected to progressive sympathectomy under aseptic precautions in successive operations under ether anesthesia. They were tested again after each stage of the sympathectomy.

Sympathectomy of the splanchnic area by lower thoracic ganglionectomy (T9 to T13) or by upper lumbar ganglionectomy (T13 to L2) and splanchnicectomy did not prevent the development of hypertension. Neither did upper thoracic sympathectomy (T1 to T6) prevent the rise in blood pressure.

When both upper thoracic (T1 to T6) and lower thoracic (T9 to T13) sympathetic ganglia were excised, the hypertension from increased intracranial pressure failed to appear. This observation has been confirmed in 4 dogs. They are being tested each month. No recurrence of hypertension was found up to 107 days.

Hypertension produced by increased intracranial pressure was slight when the heart was denervated and the adrenals removed, even though the splanchnic sympathetic innervation was intact.

Extensive sympathectomy (T5 to L5) was performed on 1 dog. The major portion of the vascular bed was sympathectomized by this procedure, but the cardiac nerves were left intact. Four days after the last operation (left, T5 to T13), hypertension did not occur when the cisternal pressure was increased. Sixteen days after the last stage, the systolic blood pressure went up from 160 to 240 mm. Hg. under the same conditions.

Conclusion. Sympathetic cardiac innervation, neural or humoral, is necessary for full development of hypertension produced by increased intracranial pressure.

The Non-specificity of Suspensions of Sodium Xanthine in Protecting the Liver Against Injury by Chloroform, and the Probable Cause of its Action. I. S. RAVDIN, SAMUEL GOLDSCHMIDT and HARRY M. VARS (Harrison Department of Surgical Research, University of Pennsylvania).

nia). In 1936 Forbes and Neale reported that they had extracted a substance from the hog's liver which exerted a marked protective action against the hepatic necrosis produced by the inhalation of carbon tetrachloride and chloroform. The active principle of their extract they subsequently reported to be xanthine. Barrett, MacLean and McHenry, and O. G. Fitzhugh have confirmed Forbes and Neale, but while Barrett and his coworkers believe that xanthine accelerates the processes of regeneration, Fitzhugh believes that it exerts a definite protective action against necrosis.

The experiments which we have conducted have been, as a rule, on rats having a fatty acid concentration of the liver by dry weight of approximately 20%. In such rats the incidence of hepatic degeneration or necrosis following 1 hour of chloroform anesthesia is about 90%. When injections of sodium xanthine, xanthine nitrate or colloidal carbon are administered 18 hours before the chloroform to rats with this concentration of liver lipid, the incidence of degeneration and necrosis following 1 hour of chloroform anesthesia is considerably reduced. When sodium ricinoleate is injected complete protection is provided even to starved rats.

The histologic picture at the site of injection varies from mild to moderate leukocytic infiltration to abscess formation. We are led to conclude that xanthine is not a specific protecting agent, but that any substance which sets into motion processes of protein catabolism in the organism will either prevent necrosis, aid in regeneration, or play a part in both. It is our opinion that the mechanism involved in these experiments is probably similar to that which has been described by Daft, Whipple and Robscheit-Robbins who found that the production of an acute sterile abscess stimulated the formation of hemoglobin in anemic dogs.

The Nature of Certain Changes in Cell Permeability Produced by Alcohols. M. H. JACOBS and A. K. PARPART (Department of Physiology, University of Pennsylvania, and Department of Biology, Princeton University). The present experiments emphasize the need of great caution in attempting to base theories of narcosis on any supposedly general permeability-decreasing or permeability-increasing effect of narcotic substances. Using concentration of n-butyl alcohol of from M/4 to M/128 at 20° C., we have found that whereas the permeability to glycerol of the erythrocytes of the rat, rabbit, guinea-pig, man and several other species is decreased, the opposite effect is obtained with those of the ox, sheep, horse, pig, dog, cat, and so on. Furthermore, even with erythrocytes of the same species the effect produced may be very different with different penetrating substances. Thus, over the range and at the temperature in question, the permeability of human erythrocytes to ethylene glycol, like that to glycerol, is decreased by n-butyl alcohol, though to a lesser extent, while that to diethylene glycol and triethylene glycol are increased; that to monoacetin is slightly decreased over a part of the range and increased over the remainder, and that to diacetin is not much changed. Permeability to none of these substances is decreased in the case of the erythrocytes of the ox. Erythrocytes of all the mammals so far studied are made more permeable

to thiourea by *n*-butyl alcohol, a substance in which thiourea is somewhat soluble, but are made much less permeable to ammonium salts of the mineral acids. The decreased permeability to the latter substances, previously inferred from observations of hemolysis, has been confirmed by direct studies, by a photoelectric method, of the pre-hemolytic volume changes of the cells. Presumably the effect is one of decreased permeability of the cell to anions, since such an effect can also be demonstrated by studies of the Cl-SO_4 exchange in solutions of sodium salts, and since it seems to be completely lacking in the case of ammonium salts of weak acids which through hydrolysis are able to penetrate cells in a non-ionic form.

The Character of Growth of Frog Carcinoma in Tissue Culture (With Motion Pictures). BALDUIN LUCKÉ (Laboratory of Pathology, School of Medicine, University of Pennsylvania). Study of tumors by the method to tissue culture has yielded much information concerning the differences between malignant cells and normal adult cells of the same type. Hitherto, such studies have been restricted to tumors of higher vertebrates. In the present paper are given results of culture experiments with a neoplasm of a cold blooded animal, the leopard frog, which is frequently affected with carcinoma of the kidney. This tumor has the appearance of adenocarcinoma, which when large not uncommonly metastasizes. The outstanding characteristic of this carcinoma is the presence of intranuclear inclusion bodies resembling those found in herpes and other diseases known to be due to viruses. The results of transmission experiments support the view that this tumor is in fact caused by filterable virus.

In the present experiments 32 such carcinomas have been cultured by the roller-tube technique of Gye and Lewis as well as by the ordinary hanging drop method. The roller tube method consists essentially in planting fragments of tissue in a thin layer of plasma attached to the inside of a test-tube. This solid medium with the explants is bathed with a nutrient liquid, which is kept circulating by slow rotation of the tube. The majority of cultures were maintained for about 6 weeks; a few were studied for as long as 16 weeks.

Under these conditions, bud-like projections promptly grow from the tumor explant into the solid medium, where they form structures resembling tubules, except for absence of a lumen. The tubules are at first contained within basement membranes, but later, proliferating epithelial cells break through the basement membrane, and spread out as thin fans of polyhedral epithelial cells. These fuse with other outgrowths of similar character until the explant is entirely surrounded by a thin flat layer of epithelium which shows no trace of differentiation into tubules or acini. It is noteworthy that in this process, stroma and macrophages take little part; the newly formed tissue is almost exclusively epithelium, indicating that it is in these cells that the exaggerated growth energy of the carcinoma chiefly resides. In common with culture of mammalian carcinoma, mitotic figures are frequent, the size of the nucleus is great relative to the cytoplasm, the nucleus is granular and the nucleoli large. However, the size of the cells of the frog carcinoma is distinctly larger than those of most mammalian tumors,

making the present material especially suitable for cytologic study. In addition, the frog carcinoma has the remarkable property of growing quite well over a relatively wide range of temperatures. The cultures flourish not only at room temperature (22° C.), but also at any temperature between 17° and 37° , with the optimum close to 30° .

In contrast to the prompt, rapid and long continued growth of this carcinoma, normal adult frog kidney in tissue culture grew only slowly and to a very limited extent. In these normal explants the epithelium especially showed low growth energy, usually being outstripped by connective tissue and macrophages.

In addition to direct observation, two cultures of the tumor were studied by cinematograph. This method not only affords a permanent record, but makes clearer the manner of outgrowth, the character of locomotion of the individual cells, as well as intracellular changes which occur so slowly as otherwise to escape detection.

Transplantation of Frog Carcinoma in the Eye of the Same and of Alien Species, Studied by Direct Microscopic Observation. BALDUIN LUCKÉ and HANS SCHLUMBERGER (Laboratory of Pathology, School of Medicine, University of Pennsylvania). The characteristics of cancer growth have hitherto been studied chiefly by histologic methods, that is in fixed, sectioned, and stained material. The recent development of slit lamp microscopy makes it now possible to observe the habit of growth of tumors while living. Carcinoma of the kidney of the leopard frog, *Rana pipiens*, has proved admirable material for this purpose. Bits of these tumors are implanted in the anterior chamber of the eye, where they soon establish themselves, and where their rate of growth may be measured, and the form of the tumor as well as the arrangement of the constituent cells may be observed through the cornea by means of the slit lamp microscope. Observation of many such transplanted carcinomas has led to the conclusion that the form which the growing tumor assumes depends on its immediate physical environment. Where the tumor grows out in the midst of the aqueous humor, not in contact with cornea or iris, there the habit of growth is characteristically tubular or papillary, the projections being hollow and cystic in some instances, solid masses of cells in others. If, however, the tumor grows in contact with an even surface such as cornea or iris, then the form of growth is entirely different; broad membranes are formed which extend along and cover the cornea or iris; such growths show no sign of tubule formation, or, at most, abortive tubules appear late in the course of growth.

The statement, so often encountered, that the growth of tumors is anarchic, and that tumors obey no laws, is not borne out by these observations. Here is a cancer, which, while growing in the frog's kidney, is typically malignant, invasive, not seldom metastasizing. Yet when transplanted in the eye, its habit of growth is distinctly influenced by its physical environment, by the nature of the space in which it grows, the surfaces with which it is in contact; in other words, this raises the question to what extent neoplastic tissues obey the same physical laws as do normal tissues.

Transplantation of tumors into other species of animals has rarely been successful. However, we have been able to grow these tumors of the leopard frog in the anterior chamber of several species, the green frog (*Rana clamitans*), the bull-frog (*R. catesbeiana*) and the toad (*Bufo americanus*). Transplanted into the eyes of these species, the tumors grew at approximately the same rate and assumed the same forms as in the original species.

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ORIGINAL ARTICLES.

STUDIES IN DYSTROPHIA MYOTONICA. I: HEREDITARY ASPECTS.

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DYSTROPHIA myotonica is of interest to workers in many fields. The neurologist, the physiologist, the ophthalmologist, the endocrinologist, the geneticist, the internist, all have something to learn from this fascinating disease. The neurologist must differentiate the muscular atrophy of this disease from other muscular dystrophies and atrophies. Although the highly characteristic pattern of the atrophy is important, that is, the almost constant involvement of the muscles of the forearm, the muscles of the face, the sterno-mas-toids, and the dorsi-flexors of the feet, the differentiation is usually made easy by the presence of the other features of the disease. The physiologist can learn much about normal and abnormal muscle behavior from the study of the myotonia which occurs in this disease. This disturbance of muscle function is characterized by a persistence of the state of contraction of a muscle after cessation of the stimuli producing the contraction; thus, if a patient grasps an object with his hand, he may not be able to release it for a number of seconds because of a persistence of the contraction of the flexors of the fingers. In this disease, myotonia is seen most commonly in the muscles of the forearm and hand, but it may be more widespread; it is rarely as generalized as in myotonia congenita (Thom-

sen's disease). The ophthalmologist is interested in the almost constant occurrence of a very characteristic type of presenile cataract. The endocrinologist ponders the apparent polyglandular involvement, so strikingly evident in most of these patients. The basal metabolic rate is usually low and the thyroid is frequently enlarged, but the blood cholesterol is normal and myxedematous deposits are lacking. Cataract and the frequent presence of a positive Chvostek suggest hypoparathyroidism, but the blood calcium and phosphorus are usually normal. Testicular atrophy and baldness are common. Geneticists have studied this disease in an effort to express the method of inheritance in classical mendelian terms. A disease of such varied manifestations must belong in final analysis to the internist who interprets each of the many signs as evidence of the presence of a "more widespread morbid process."

Study of the inheritance of the muscular dystrophies serves as a valuable aid in the nosological distinction of these diseases. Clinical distinction between two very similar diseases may be confirmed by the demonstration of different types of inheritance. This fact has been stressed by Barker¹ who cites as an example the case of the similar but clinically differentiated Erb-Duchenne and Landouzy-Dejerine types of muscular dystrophy. In a muscular dystrophy, probably of the Erb-Duchenne type, studied by Minkowski and Sidler,¹⁷ the inheritance is of double mendelian recessive nature. The Landouzy-Dejerine type of muscular dystrophy, however, exhibits mendelian dominance. A similar observation can be made in the case of dystrophia myotonica and myotonia congenita. These diseases, confused for many years because of the occurrence in both of myotonia, have been separated on the basis of clinical findings. Again we find that differences in the methods of inheritance justify the separation of these diseases. Myotonia congenita, as the studies of Nissen¹⁸ show, is transmitted as a pure mendelian dominant. Nissen, tracing the disease in his own family from 1740, was able to show that the disease was inherited without interruption from one generation to another; myotonic descendants were always from myotonic parents and in no case did one find an individual without myotonia whose descendants showed myotonia. On the other hand, dystrophia myotonica occurs commonly in the children of apparently normal parents, and is infrequently seen in two successive generations. Dystrophia myotonica exhibits what appears to be a very irregular type of inheritance. The nature of this inheritance is the object of this report.*

* We are familiar with the work of Boeters⁴ in which the author presents a number of pedigrees to prove the occurrence of both dystrophia myotonica and myotonia congenita in the same families and concludes that the two diseases are different external manifestations of the same inherited defect. We feel, however, that he has failed to differentiate clearly the two diseases. He divides the cases into those with myotonia alone, which he calls myotonia congenita, and those with myotonia associated with dystrophic and endocrine anomalies, among which he places dystrophia

Description of Families. B. FAMILY (Figs. 1 and 2). *Generation I.*—All born in America. 2* believed to have been of Scotch ancestry, 3 of "Pennsylvania Dutch," and 4 of Scotch-Irish.

Generation II.—Nothing remarkable.

Generation III.—1. M. W. B., aged 62; weakness and atrophy of muscles of forearm and hand for over 14 years; myotonia in handgrasp for 4 or 5 years; difficulty in walking for over 10 years; intolerance to cold; baldness; typical "myopathic" facies; marked atrophy of the sterno-cleido-mastoid muscles and the muscles of the forearms and hands; mechanical myotonia in the tongue and hand muscles.

2. J. B., aged 60; weakness of the handgrasps for at least 13 years; difficulty in walking for several years; generalized weakness and loss of weight in recent years; baldness; typical "myopathic" facies; testicular atrophy; early cataract bilaterally; generalized muscular atrophy; voluntary myotonia in handgrasps; myotonic reaction in muscles of forearm and hand.

Generation IV.—3. R. B., aged 27; weakness in handgrasps first noticed 10 years ago; some difficulty in walking noticed in last year; intolerance to cold; loss of facial expression; early cataract bilaterally; testicular atrophy; marked atrophy of sterno-cleido-mastoids; voluntary myotonia in handgrasps; myotonic reaction in muscles of forearm and hands.

4. M. J. B., aged 20; voluntary myotonia in handgrasps since the age of 13; some weakness and atrophy of the sterno-cleido-mastoid muscles; early cataract present bilaterally; mechanical myotonia in tongue muscles and muscles of forearms and hands.

M. FAMILY (Fig. 3). *Generation I.*—1 and 2 are believed to have been born in America. 4 and 5 came from Germany.

Generation II.—1 did not talk plainly. 5 had a cataract operation at 65 years. 6 began to have cataracts at about 50 years and was operated upon for them at about 60 years. 12 was an invalid for the last 35 years of her life and was unable to leave her wheel chair for many years before her death at 64 years. An obituary note states that she had "locomotor ataxia."

Generation III.—18. N. M., aged 59; myotonia in handgrasps for 7 years; difficulty in walking for 1½ years; cataracts for at least 13 years; marked atrophy of the sterno-cleido-mastoid muscles; myotonic reaction in muscles of the forearm and hand.

myotonica. This seems a false division for the following reasons: (1) The presence of myotonia alone does not mean that the case may not be one of dystrophia myotonica, for it is well recognized that early in the course of this disease the myotonia may be the only symptom. (2) Myotonia with dystrophic signs of irregular pattern and type does not constitute the syndrome of dystrophia myotonica. Dystrophia myotonica presents a clinical picture almost monotonous in its uniformity.

This false division may completely distort the interpretation of a pedigree as will be seen by examination of the pedigree of Boeters' Case 1. In this family are found 10 cases of myotonia, 7 of which Boeters classifies as myotonia congenita and 3 of which he classifies as myotonia with dystrophic and endocrine anomalies. We see no reason for this division and think all the cases in this family are myotonia congenita because: (1) In the 10 cases there is no single case of muscular atrophy or of cataract. (2) In our experience the presence of atrophy and cataract in dystrophia myotonica has been more constant than the presence of myotonia. (3) The ages of onset are stated to be about 20 years in 1 case, in "youth" in 3 cases, and in the other cases 13, 12, 11, before 10, 4 and 3 years of age: the earliest age of onset in the pedigree, 3 years, occurred in the mother of 8 of the cases. This onset of the disease in youth in practically every case is the expected finding in a pedigree of myotonia congenita and varies markedly from the experience of workers on dystrophia myotonica as seen in Table 1.

*The numbers in italics refer to the members of the generation indicated. In the figures these members are numbered consecutively from left to right.

19. J. L., aged 56; myotonia in handgrasps for the last 8 years; some difficulty in walking up steps during the last few months; incipient cataracts found 3 years ago; mechanical myotonia in muscles of tongue, forearm and hand.

20. C. M., aged 53; clamping of hands on tools; no other symptoms or findings.

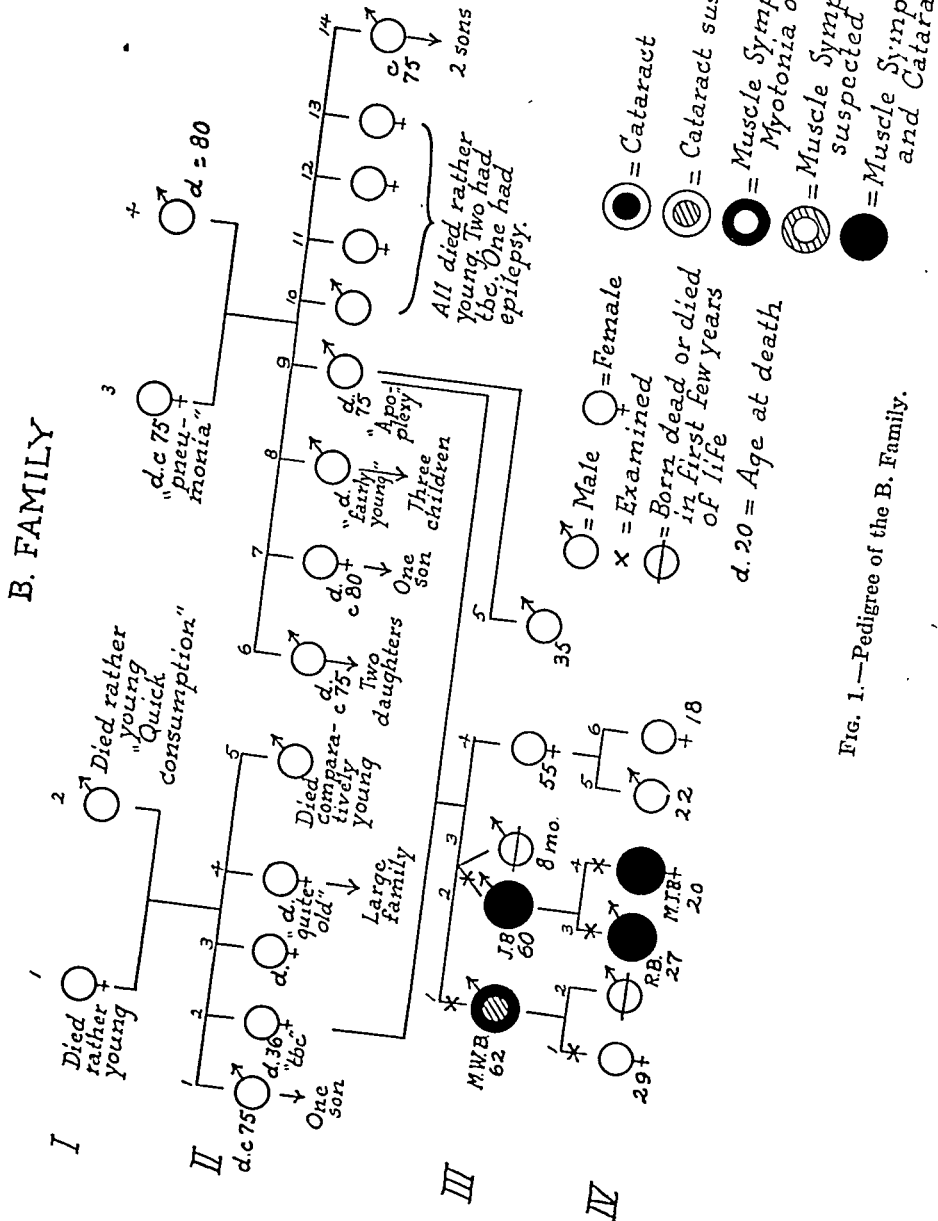


Fig. 1.—Pedigree of the B. Family.

25. O. M., aged 43; some weakness in his hands since age of 27; told he had cataracts at 30; noticed myotonia in handgrasps at 33 and in legs during last 4 or 5 years; intolerant to cold; "hatchet" facies; "steppage" gait; testicles atrophic; myotonic reaction in muscles of forearm and hand.

Generation IV.—17. H. M., aged 22, has cataracts of the type described as typical for dystrophia myotonica.

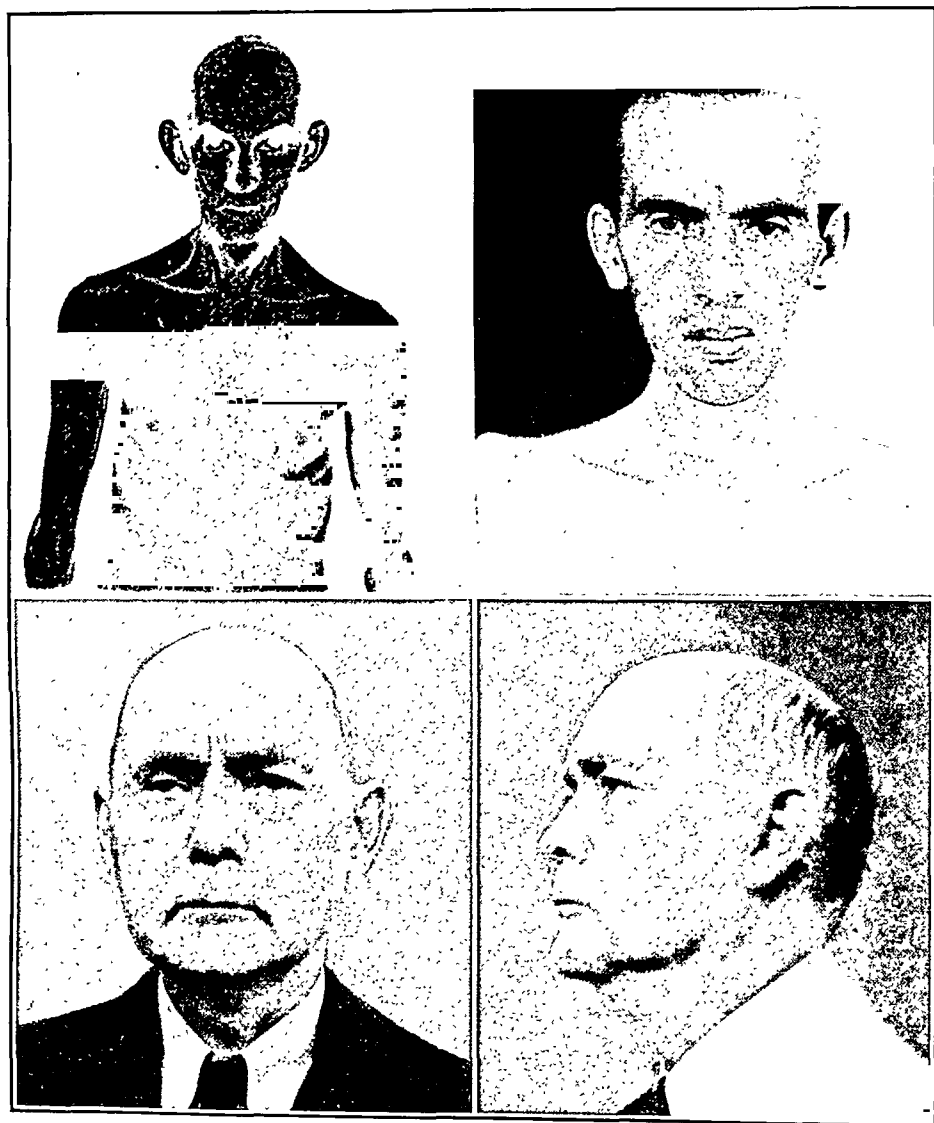


FIG. 2.—Some members of the B. Family. Upper left, J. B. (III 2 in Fig. 1). Upper right, R. B. (IV 3), son of J. B. Lower right and left, M. W. B. (III 1), brother of J. B.

PF. FAMILY (Fig. 4). Generation I.—1 and 3 were born in America. 4 and 5 were born in Germany.

Generation II.—6 was operated upon for cataract at about 55 years of age. He died of diabetes but had diabetes only a few years before his death.

Generation III.—2. N. Pf., aged 54; myotonia in handgrasps for 15 years; weakness of handgrasps, especially in last 9 years; "slapping" gait

for about 5 years; cataract operation 2 years ago; baldness; marked atrophy of muscles of forearm and of sterno-cleido-mastoid muscles; myotonic reaction in muscles of forearm and hand; "myopathic" facies.

3. R. Pf., died at about 33 years of "heart attack"; cataract operation at 30 years; trouble with hands and legs for several years before his death.

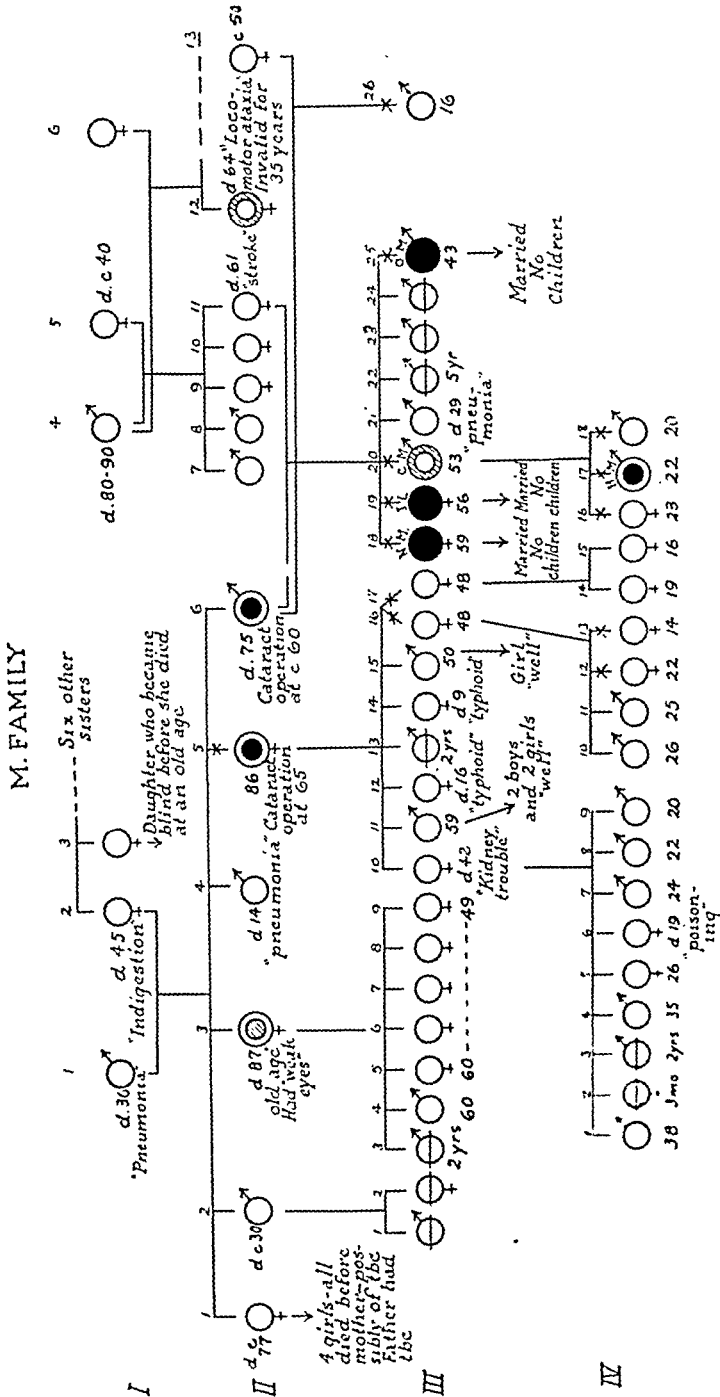


FIG. 3.—Pedigree of the M. Family. (Legend as in Fig. 1.)

4. M. S., died at 42 years following an operation for an abdominal tumor; cataract operation at 37 years; trouble with hands for several years before death.

5. R. R., aged 48; marked difficulty with hands for a number of years; cannot walk very well; difficulty in talking; poor vision for years.

D. FAMILY (Fig. 5). Except for some members in *Generation IV*, all members of this family were born in Sweden.

Generation I.—Nothing remarkable.

Generation II.—14 had cataract operation at the age of 61 and again at 64.

15 died at 50 years following a cataract operation. She is said to have been deaf and dumb as a result of a childhood disease.

Generation III.—2. J. M., aged 46; myotonia present for 23 years; weakness of hands moderate in last 13 years; difficulty in walking for last 3 years; cataract operations 8 and 5 years ago; "myopathic" facies; marked atrophy of sterno-cleido-mastoid muscles; myotonic reaction in muscles of forearms and hands.

8. S. E., aged 34; has no complaints but has typical early cataracts.

9. Mrs. J., aged 31; has been operated upon for cataracts in the last year.

Discussion. The classical investigations of Fleischer^{6a} in 1918 confirmed and emphasized the hereditary nature of dystrophia myotonica. The details of the method of inheritance have been determined slowly and can be expressed today in terms familiar to the experimental geneticist.

The fact that the parents of most patients with dystrophia myotonica are apparently normal suggests a recessive inheritance. The following observations, however, indicate that the factor responsible for the disease acts as a mendelian dominant:* (1) if the disease were recessive, the number of consanguineous marriages among the parents of the affected patients should be greatly increased since, in this case, the rarer the character in the general population, the more often will it be found that persons exhibiting the character are the offspring of the marriages of near kin.² Consanguineous marriages, however, are infrequent among the parents of patients with dystrophia myotonica. Not one occurred in any of our families. In his remarkable investigation of an affected family through six generations, Fleischer^{6b} found no evidence that consanguineous marriages played any part in the manifestation of the disease. (2) Once the disease has become manifest in a family, affected individuals transmit it to their children. All instances of such trans-

* The two contrasting characters that are produced by the two differing members of a pair of chromosomes are spoken of as allelomorphs. The dominant character is that member of the pair of allelomorphs which, when both contrasting characters are present, predominates over the other, the recessive character, in its manifestations. The recessive character will, therefore, not be manifest unless present by itself, that is, in both members of the chromosome pair. When a character is present in both members of the chromosome pair, the individual is homozygous for that character. If the character is present in only one of the chromosomes, the individual is heterozygous for that character. In speaking of "dystrophia myotonica" as a dominant character, the contrasting or allelomorphic character is, of course, "normal." Since the chromosome pairs of the child are made up of one from each of the parents, a recessive character will become manifest only if each of the parents transmits it to the child. A dominant character, however, will be manifest in the child if only one parent transmits it.

mission which could be found in the literature have been tabulated in Table 1. Direct transmission of a disease from parent to child is strongly suggestive of dominant heredity, because, in the case of a dominant character, only one parent in each generation need transmit the defective gene; whereas, in the case of a recessive character, both parents in two successive generations must transmit the defective gene. If the disease is rare, the chance meeting in two succes-

Pf. FAMILY

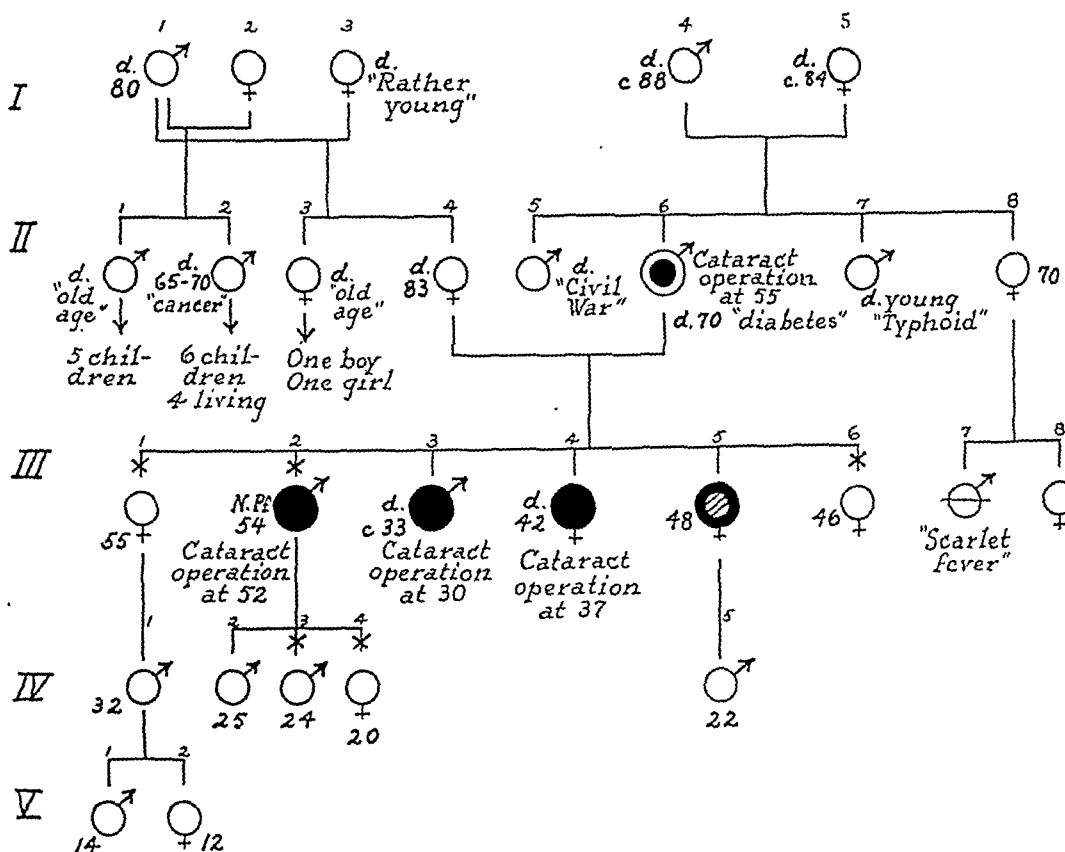


FIG. 4.—Pedigree of the Pf. Family. (Legend as in Fig. 1.)

sive generations of carriers of the disease gene is very unlikely. In the B. family (Fig. 1), if the gene is recessive, not only J. B. and his parents must be considered as carriers of the gene, but also the wife of J. B. (3) Maas,¹⁵ Boeters⁴ and Kolb *et al.*¹³ report the occurrence of the disease in half brothers and sisters. A recessive character would require the participation of three carriers and, therefore, would be very unlikely. In the case of a dominant character, only the common parent need be affected. (4) Henke and Seeger's¹² investigation of their own material and the sibships reported in the

literature indicated that the percentage of affected individuals in the sibships was very close to 50. This was true in sibships of an affected parent as well as in sibships of apparently normal parents. This is the expected percentage in the case of a single factor dominant inheritance where the parent is heterozygously affected. In a

D. FAMILY

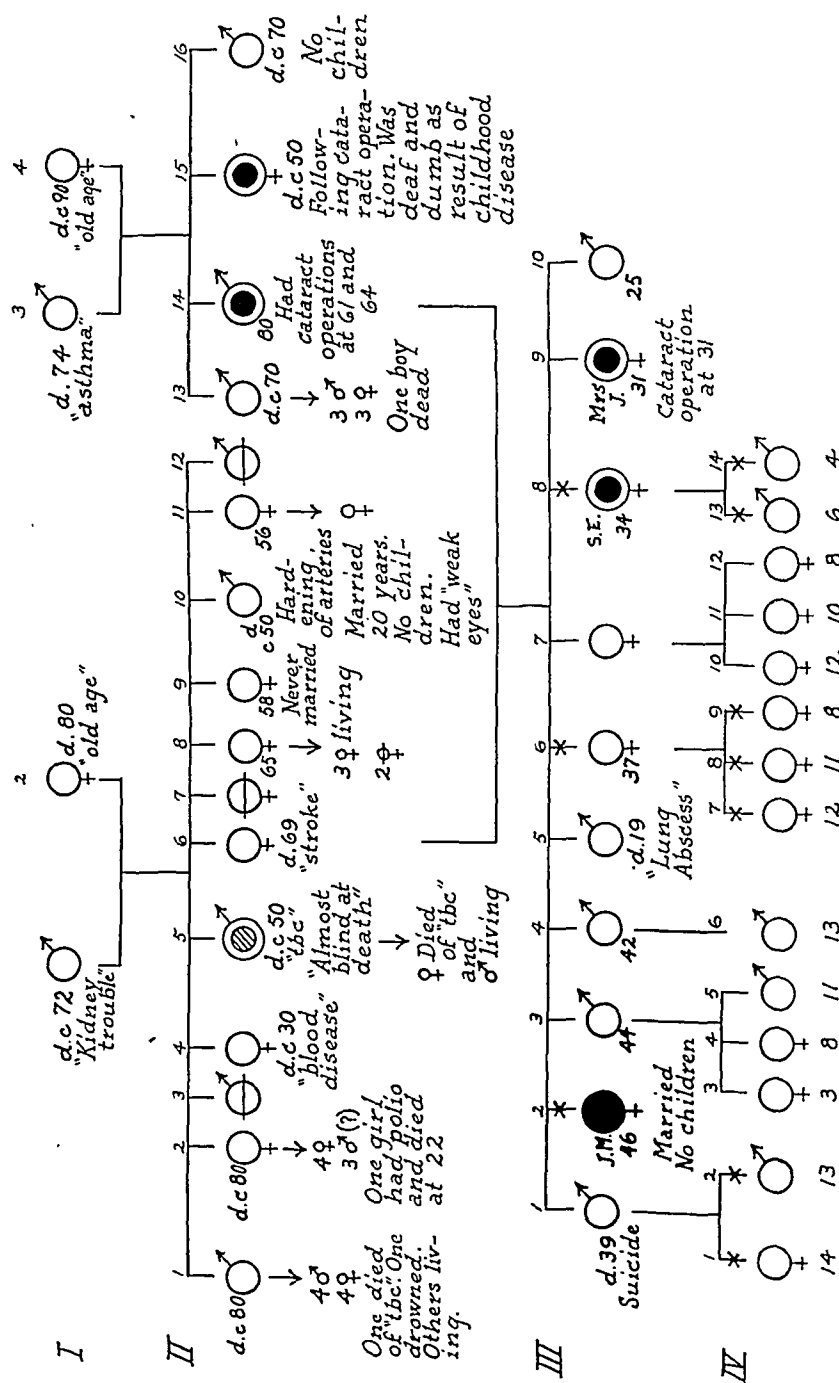


FIG. 5.—Pedigree of the D. Family. (Legend as in Fig. 1.)

rare disease the number of homozygously affected individuals would be too small to be significant. With a single factor recessive inheritance, only 25% of the siblings should be affected if the parents are apparently normal but heterozygous. Where one of the parents is affected the percentage of affected children would be 50 if the other parent is a carrier and zero if the other parent is normal. If a group of affected parents are considered, however, the percentage of affected children would be very small because the number of marriages of affected parents to normal individuals would greatly exceed the number of marriages to carriers of a rare disease. The percentage of affected individuals in the sibships in our pedigrees is over 50 and is probably explained by the error inherent in small numbers and the selection of material which results because the greater the number of affected individuals in a sibship the more apt the sibship is to come under observation. If those cases labeled suspicious are considered as unaffected, the percentage of affected individuals in the families studied by Maas¹⁵ is 60.

These observations would seem to leave little doubt concerning the dominant inheritance. That this dominance is not typical, however, is obvious from the fact that the parents and grandparents of most of the patients are normal. A dominant factor may apparently skip a generation; but the occurrence of unaffected parents is too general to be explained in this manner. We have, therefore, a strong argument for a modified dominant inheritance. Investigation of the causes for the infrequency of the occurrence of dystrophia myotonica in two or more generations furnishes a clue to the nature of the modification. The causes probably are as follows: (1) Patients with the disease show a marked infertility and, therefore, have few descendants. Of 10 individuals, including 3 in the Pf. family not examined but unquestionably affected, who showed evidence of moderate or severe muscular signs and who were married, 5 have had no children and the remaining 5 have a total of 8 children (distributed as follows: 3, 2, 1, 1, 1). Since only 4 of these children may be expected to develop the disease and the 4 cases can occur in as few as 2 or 3 sibships, it is evident that of the original 10 cases only 2 to 4 are likely to have children with the disease. This number may be further decreased by the failure of the children to reach an age necessary for the disease to become manifest. (2) Examination of Table 1 reveals the very interesting and important fact that in every case, without exception, the age of onset of the disease in the children was at an earlier age than in the parents. This phenomenon, which will be discussed later, has been observed in other hereditary diseases and called the "law of anticipation." If the onset of the disease in an individual occurs at an age at which

he has already had children, his children and certainly his grandchildren will develop the disease at an age which will prevent further propagation. This becomes even more likely because of the frequently observed increasing severity of the disease in each succeeding generation.*

These observations in regard to the earlier age of onset and increasing severity of the disease in succeeding generations suggest an explanation for the occurrence of the disease in the children of apparently normal parents. It appears possible that the parent who carries the anlage for the disease either may have the disease in a very mild form or may not live long enough for it to develop. The first individual in a family who shows the complete syndrome usually manifests it in the third or fourth decade, and by the time medical advice is sought the parents usually are either dead or for other reason are not available for examination. Study of pedigrees reveals in the ancestors, however, the frequent occurrence of cataract, one of the most characteristic signs of dystrophia myotonia. Fleischer^{6a} has offered evidence that the occurrence of this cataract also presents the remarkable phenomenon of anticipation; that is, the age of onset is earlier in each succeeding generation. In the early generations occur senile cataracts, in later generations presenile cataracts, when the complete syndrome appears the cataracts may occur in youth. In the pedigree here reported it will be noted that one of the parents of each of 3 affected sibships was operated upon for cataract (at ages of 55, 60 and 61) and 2 aunts were operated upon for cataract (at ages of 50 and 65). The parents of dystrophic patients appear, therefore, to manifest the inherited defect but in a limited form. Careful investigation of these individuals possibly would show that they have other mild evidences of the disease, as suspected by Curschmann^{5b} and proved by several case histories in Maas' article.¹⁵

We may summarize this discussion as follows: The disease appears to be due to a dominant mutation, which is at first manifest by no signs or by very slight and few signs, notably cataract. The gene may be transmitted through several generations with no apparent manifestations, as shown by pedigrees in which apparently scattered cases of dystrophia myotonica may be traced back six or seven generations to a common ancestor. In those families where cataract occurs, its onset at an earlier age in succeeding generations is evidence of the presence of the defective gene. Finally, in one generation the disease becomes severe enough and sets in early enough to be clearly recognized. Individuals with the disease now transmit it to their children as a simple dominant. The onset of the

* In comparing severity of a disease it must be remembered that the duration of the disease is important and that the comparative severity of the disease at the time of examination is not a true gauge.

disease in the children is at an earlier age than in the parents until, finally, a generation occurs in which the onset is before an age at which the patients mature and the disease ceases to appear in that family.

The phenomenon of increase in severity of disease in succeeding generations has been called "potentiation." For the phenomena of anticipation and potentiation the term "progressive inheritance" has been used. Some authors have denied the existence of anticipation, claiming that it is a statistical error which results from the fact that the material is selected. They say that only those members of earlier generations who live long enough to become parents are considered; whereas, in later generations those who might develop the disease at an older age are not considered. This may be true when one analyzes mass statistics, but is not true, as pointed out by Macklin,¹⁶ in the case of completed pedigrees, such as, for example, was used by Henke and Seeger.¹² The latter suggest three possible explanations for the phenomenon of progressive inheritance: (1) a progressive change in the germinal cell plasm alone, (2) an inherent tendency of the gene conditioning dystrophia myotonica to change continuously and (3) repeated changes in the gene as a result of somatic influences.

On the basis of certain properties of genes which have been determined by recent investigations, we have constructed a hypothetical picture of the process of progressive inheritance. Investigations of Goldschmidt⁹ and others indicate that the different behavior of allelomorphs depends, in many if not all cases, on a difference in degree of activity rather than in kind of activity. (See footnote page 599 for definition of allelomorphs.) In the case of many genes a mutation means, therefore, a change to a new level of activity at which the gene usually remains. One would seem justified in assuming that in the case of degenerative disease the gene change may consist of loss of activity. Moreover, this loss of activity is assumed to be of such nature that once begun it progresses slowly but continuously over a period of many years. (See above, Henke and Seeger's second possibility.) Some justification for this latter assumption is found in the observations⁹ that in certain plants the changes in the gene are not stable and may occur at various levels in a haphazard manner. The degree of change in the gene in the individual in whom the mutation first appears, and possibly in his children and grandchildren, may be so small that no symptoms or only very mild symptoms occur. Over a period of several generations, however, the activity of the gene is so greatly diminished that although associated with a normal gene, the combined activity is not sufficient for normal function and various degenerative signs appear. In the succeeding generations, the gene activity is further decreased, so the onset of the degenerative change is at an earlier age and more severe in character.

In addition to generational anticipation, some authors speak of a "fraternal anticipation"; that is, the disease appears to have its onset earlier in the younger siblings of a sibship. Although this phenomenon does not appear as regular in its occurrence as the generational anticipation, it is strikingly evident in many of the sibships reported.

Since an approximate 50% incidence of the disease in affected sibships is to be expected with a single dominant factor, we have thus far considered dystrophia myotonica as determined by the presence of a single gene. The occurrence in sibships of cases with muscle symptoms alone, or with cataract alone, or with the two conditions combined has led to the suggestion that we are dealing with linked factors; that is, different genes, each producing some phase of the disease, located in the same chromosome. It is obvious that any dissociation of the signs of the disease that occurs in such case would have to be explained by crossing over; if no crossing over occurred, the linked genes would always occur together and be indistinguishable from a single gene.* That the condition is probably due to a single gene or to several genes so closely linked that crossing over is of very little importance, appears from the following considerations: (1) The vast majority of those affected, if carefully examined and followed over a period of years, sooner or later show all the manifestations of the disease. Many individuals who at the time of their first examination show only one symptom, develop the others later. (2) The complete syndrome may occur in children of parents who show only one of the signs. In Family M. (Fig. 3), for example, H. M. at present has only cataract although his father has myotonia and no cataract (slit lamp examination). (3) If crossing over and consequent dissociation of the symptoms of the disease were very frequent in early generations, the complete syndrome would not occur so frequently and individual symptoms so infrequently in later generations.

The variations in the manifestations of the disease and the special prominence of cataract may be explained as follows: It is now commonly recognized that each gene, although it may most markedly affect one organ or tissue, has an influence in the development of a number of tissues or organs;² furthermore, each of the tissues or organs affected by this gene is also affected by numerous other genes. Diminution in the activity of the gene, therefore, affects many tissues. The degree to which each tissue will be affected will depend on the pattern of the other genes affecting that tissue; thus the diversity in the manifestations of the disease. When the action of the gene is only mildly defective, only those tissues will show

* Since genes which exhibit linkage do so because they are located in the same chromosome, a break in the linkage can be caused only by an interchange of parts between members of a pair of homologous chromosomes. The mechanism of interchange of parts is called "crossing over."

TABLE 1.—SUMMARY OF CASES IN WHICH DYSTROPHIA MYOTONICA HAS OCCURRED IN TWO SUCCESSIVE GENERATIONS.

(In the middle columns with the boldface figures the probable age of onset of the disease in parent and children may be contrasted.)

Authors.*	Parents.						Children.					
	Case designation.	Age. ⁺	Sex.	Examined or not examined.	Severity. [†]	Probable age of onset. [‡]	Probable age of onset.	Severity.	Case designation.	Age.	Sex.	Examined or not examined.
Curschmann (1912)	J. B.	55	M	E	S	42	21	M	J. E. B.	33	M	E
Grund (1914)	M. Pf.	47	F	E	L	18	10	M	L. Pf.	28	M	E
							10	S	W. Pf.	20	M	E
Kyrieleis (1925)	Mother P.	71	F	E	M	45	28	S	P. P.	43	M	E
							20+		Sister P.	39d	F	NE
							30	M	A. P.	36	M	E
Heine (1925)	L. W.	43	F	E		34	<19		W. W.	21	M	E
Frey (1925-26)	G. A.	52d	M	NE	S	30+	14	S	EA.	35	M	E
	M. J.	58	M	E	S	<30	25	S	M. J.	31	M	E
							17	S	F. J.	30	M	E
	G. M. M.	58	M	E		30+	20	S	H. J. M.	23	M	E
Henke and Seeger (1927-28)	E II 7eβ		M	E	L	48	17		E II 7eβl'		M	NE
	E II 7fe		F	E	M	34	7-14	S	E II 7fel'		M	E
	E III 6a		M	E	L	50?	<26	S	E III 6aκ		M	E
							40?	L	E III 6aη		M	E
	F II 10g		F	E	L	<50	<27	S	F II 10gβ		F	E
							<32		F II 10gδ		M	E
							<21	S	F II 10gε		M	E
							<18	S	F II 10gη		M	E
	Sch.		F	E	M	35	<18	S			F	E
							<15	S			M	E
							<13				M	NE
Gifford <i>et al.</i> (1929)	Mrs. L.	43	F	E	M	33	13	L	L. L.	18	F	E
Bielschowsky <i>et al.</i> (1933)		61d	M	E	S	35+	18	S	W. Raf.	41d	M	E
Maas (1937)	S. B. (II)	50	F	E	L	<50	In-fancy	S	SB (III)	26		E
	D (II)	50	M	E	M	35	<22		D (III) 1	22	M	E
							<19		D (III) 2	19	F	E
	D I	76	F	E	L	<76?	35	M	D (II)	50	M	E
	Mrs. C.	59	F	E	L	40	<26			26		E
	Mrs. G.	48	F	E	L	<46?	<24	L	L	24	M	E
							19	L	V	21	F	E
							<17	L	D	17	F	E
							13	L	H	14	F	E

TABLE 1.—Continued.

Maas (1937) (Continued)	FTAR	50	M	E	S	30	<28		1			
							<23		3			
							<20		4			
							<18		6			
							<15		7			
							<13		8			
	J. McD.	56	M	E		20	18	S		25	M	
							10	S		17d	M	E
							8	S		14	M	
	H. D.	53		E		37	<23		Ellen	23	F	E
	P. B.	53		E		36	16			24	F	E
	Mrs. C.	43	F	E	L	<43	<19	L		19	F	
	J. G.	55	M	E	S	50	<32	L	Ada	32	F	E
	P. B.	46	M	E	S	30	7	S	B. B.	18	M	
	Karl S.	53	M	E		<53	<24		W. S.	24	M	
	K. R.	51	F	E	S	<48	<28	L		28	F	
							<21	S		21	M	
	Mrs. A.	55	F	E	S	<31	10	S		29	F	E
	Mrs. W.	50	F	E	L	<32	<18	S		18	F	
							<13	S		14	M	
	Mrs. D.	58	F	E	L	<52	<24	M		24	F	
							<19	S		19	M	
Ravin and Waring (1938)	J. B.	60	M	E	S	47	18	M	R. B.	27	M	E
							13	L	M. J. B.	20	F	E

* Boeters' cases have not been included for the reasons given in the footnote, page 594.

+ "d" after the age indicates that the patient was dead at the time of the report.

† "S" = severe case. "M" = moderately severe case. "L" = light case.

‡ The exact age of onset of this disease is difficult to determine and in many cases the authors have been vague. At best, therefore, the ages given are approximations. The sign "<" has been used to indicate "less than," and "?" has been used when there was some doubt regarding the diagnosis.

involvement in which the other factors are of such a nature as to predispose to the manifestation of the defect. When the gene is markedly defective most of the tissues affected by the gene will show involvement regardless of the nature of the modifying factors. In the case of cataract we may assume a modifying factor, widely distributed, which by itself produces no lens changes, but which will produce cataracts in the presence of a mildly defective dystrophia myotonica gene, too mildly involved to produce other symptoms. If this modifying factor is present, cataract occurs as an early symptom; if the modifying factor is absent, cataract may not occur in fairly marked cases of the disease.

Most studies of sex incidence have shown a preponderance of males but not to a degree suggesting sex linkage. Several of the

more complete studies have shown an equal incidence of the sexes. A preponderance of males in smaller series not completed by family investigations probably results from the following circumstances: (1) Men are more likely to present themselves to a doctor because the disease affects their working ability. (2) If a man is affected, his economic status becomes such that he is likely to be seen in a clinic; whereas, when the woman is affected the economic status of the family is not changed, and she is more likely to be seen by a private doctor.

Certain clinical criteria have been advanced for a group of diseases known as the heredo-degenerative diseases. These criteria are: (1) The disease affects as a rule several members of the same generation in the same manner. This has been called "homologous" heredity. (2) The onset of the disease in the members of the same generation is at about the same age. This "homochromous" heredity is, of course, in contrast with "fraternal anticipation." (3) The basis of the disease is endogenous. (4) The disease progresses irresistibly from the moment of its onset. It is evident that dystrophia myotonica fulfills these criteria and belongs in the group of heredo-degenerative diseases. The explanation of these criteria in terms of mendelian inheritance is also clear.

Families in which such degenerative diseases occur have been thought to show degenerative stigmata; that is, members who do not show the disease may show other stigmata, such as mental or physical inferiority, epilepsy, sterility, and so on, which may be considered degenerative. By comparing the number of such stigmata in a family in which dystrophia myotonica was traced through several generations with the incidence in a comparable normal family, Henke and Seeger¹² came to the conclusion that the incidence of these conditions was not increased in the dystrophic family and that these conditions had nothing to do with the anlage for dystrophia myotonica.

Summary. 1. Dystrophia myotonica, a disease belonging to the heredo-familial group of diseases, affects many tissues and organs of the body and is of interest to workers in many fields of medicine.

2. Four family trees in which the disease occurs are presented. In these family trees, 12 cases of dystrophia myotonica were found among 33 members examined. At least 4 additional cases of the disease occurring in the family could not be investigated.

3. A table is presented in which most instances to be found in the literature of direct transmission of the disease from parent to child are tabulated. This table shows strikingly that in all of these cases the onset of the disease in the children was at a definitely earlier age than in the parents.

4. Evidence leads to the conclusion that dystrophia myotonica

is transmitted as a single factor dominant but that this dominance is modified by the occurrence of "progressive inheritance." In "progressive inheritance" the onset of the disease is at an earlier age in each succeeding generation (anticipation) and the disease increases in severity in succeeding generations (potentiation).

5. Because of the presence of progressive inheritance, on the one hand the parents of many patients may show little or no signs of the disease, and on the other hand the children of patients tend to develop the disease so early as to prevent further propagation and the diseases dies out in the family.

6. Possible changes in the germinal material which could produce this type of heredity are described.

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THE CHEMOTHERAPY OF EXPERIMENTAL TYPE II PNEUMO-COCCIC MENINGITIS.

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FOLLOWING the demonstration of the efficacy of sulphanilamide against experimental pneumococcic infections in mice by Rosenthal¹⁹ and by Cooper, Gross, and Mellon,⁷ the latter investigators^{5a,b,8,a,b} demonstrated an even greater therapeutic action against experi-

mental pneumonia caused by Types I, II, and III pneumococci in rats. In these experiments, sulphanilamide therapy appeared to be equal to, or better than, optimum serum therapy and the combination of the two more efficacious than either alone against rat pneumonia produced by Types I and II pneumococci. Furthermore, it was shown independently by us^{8b} and by Branham and Rosenthal² that sulphanilamide and serum acted synergistically in pneumococcic infections. On the basis of these experimental results, it was suggested that sulphanilamide be tried in human pneumonia, either as an adjuvant to serum therapy, or in the absence of serum, as the primary therapeutic agent. The Special Report of the Pneumonia Advisory Committee to the Surgeon General²³ contains a similar recommendation.

In spite of repeated demonstrations on mice, rats and rabbits which showed the effectiveness of sulphanilamide in experimental infections caused by pneumococci of Types I,^{2, 8b, 11, 14, 19, 20, 25} II,^{5b, 6a, 19, 20} III,^{5a, 7, 8a, 19, 20} VII,^{6b} and XIV,²² various authors have neglected to mention any type other than Type III as being susceptible to sulphanilamide therapy in either animals or man.

Clinical corroboration of the experimental results was initiated with the report by Heintzelman, Hadley, and Mellon⁹ dealing with sulphanilamide therapy of Type III pneumococcic pneumonia. This has been followed during the past year by other publications which tended to demonstrate the efficacy not only of sulphanilamide but also of other sulphonamide derivatives in clinical pneumonia,^{1, 15} meningitis,^{1, 10, 12, 13, 16-18, 24} and other infections caused by pneumococci.^{3, 4, 21}

Inasmuch as pneumococcic meningitis in man has an extremely high fatality rate,¹⁸ it was thought of interest to obtain data on the susceptibility of experimental pneumococcic meningitis to therapy with sulphanilamide* and 4,4'-di-(acetylamino)-diphenylsulphone.†

In a preliminary publication we^{6a} recently indicated that sulphanilamide is very effective in Type II pneumococcic meningitis of rats. In the present report, the detailed findings in a series of 115 rats with Type II pneumococcic meningitis, treated and untreated, are presented.

Method. White rats were anesthetized with ether and a 25-gauge hypodermic needle, 3 mm. long, attached to a tuberculin syringe was pushed to the hilt through the intact skin and skull at a point about 5 mm. lateral to the sagittal suture and midway between eye and ear. The inoculum, consisting of 0.1 cc. of diluted 18-hour broth culture of a Type II pneumococcus (Binda strain), was then slowly injected and any leakage removed with a phenolized swab.

In the following three experimental series, different infecting

* Kindly supplied by E. R. Squibb & Sons, New York.

† Synthesized and donated to us by the Monsanto Chemical Company, St. Louis, Missouri.

doses and different periods of delay between infection and the initial treatment were employed.

1. Experiment With a Moderate Infecting Dose and a 6-hour Delay in the Initial Treatment. A group of 54 rats was infected with a 10^{-5} dilution of a culture corresponding to about 10 fatal doses, as indicated above. Two rats infected with a 10^{-6} dilution of the same culture died in less than 93 hours. Three hours after the infection, 2 rats were sacrificed and smears made of the heart blood and the lower lumbar portion of the spinal cord. The spinal cord cultures were both positive, whereas only one of the two heart blood cultures was positive. No pneumococci were seen in either of the blood smears or smears of the spinal cord (meninges) although the latter showed numerous neutrophils and some monocytes. Five hours after the infection, or 1 hour prior to the initial treatment, 2 more rats were sacrificed. Both of these gave positive heart blood and positive spinal cord cultures. Smears of the cord (meninges) of both animals showed in addition to numerous neutrophils and some monocytes, also a few pneumococci.

The initial treatments, begun 6 hours after the infection, consisted of oral doses of 100 mg. of sulphanilamide as a 20% suspension in 15% aqueous gum acacia for 15 animals. Doses of 100 mg. of 4,4'-di-(acetylamino)-diphenylsulphone, similarly suspended, were administered to 15 other rats. The remaining 20 animals were not treated and served as controls. These doses were given twice daily for 2 days and then once daily for 8 subsequent days.

All survivors were sacrificed 22 days after infection and cultures and smears made of the heart blood and distal portion of the spinal cord (meninges). The spine with attached skull was removed and fixed in formalin, after which the brain and cord were carefully dissected and sections, stained with hematoxylin and eosin, were made. Similar procedures were followed with all the fatalities.

Results. The results are shown graphically in Figure 1. While the fatality rate in the control group was 100% and 60% in the sulphone group, the sulphanilamide-treated group showed only a 26.7% fatality. Similar differences were found in the average survival time of the fatalities which was $36\frac{1}{2}$ hours for the control group, 68 hours for the sulphone group, and $8\frac{1}{2}$ days for the sulphanilamide group.

In the control group all blood and spinal cord cultures were positive. Of the fatalities in the sulphone group, all blood cultures and all but one of the spinal cord cultures were positive, while of the 4 sulphanilamide treated fatalities, 3 showed positive blood cultures, and only 1 a positive spinal cord culture. All survivors gave negative blood and spinal cord cultures.

2. Experiment With a Heavy Infecting Dose and a 6-hour Delay in the Initial Treatment. A series of 45 rats was infected with a 10^{-4} dilution of the same culture as in Experiment 1, using the same

technique. This dilution corresponded to about 100 fatal doses. Treatments identical with those of the preceding experiment were initiated 6 hours following the infection and continued daily for 10 days, with 2 daily treatments on the first 2 days. There were 15 rats each in the control, the sulphone, and the sulphanilamide groups. Cultures and smears of the heart blood and spinal cord, as well as sections of the brain and the spinal cord were made of all fatalities and of the survivors which were sacrificed after 22 days.

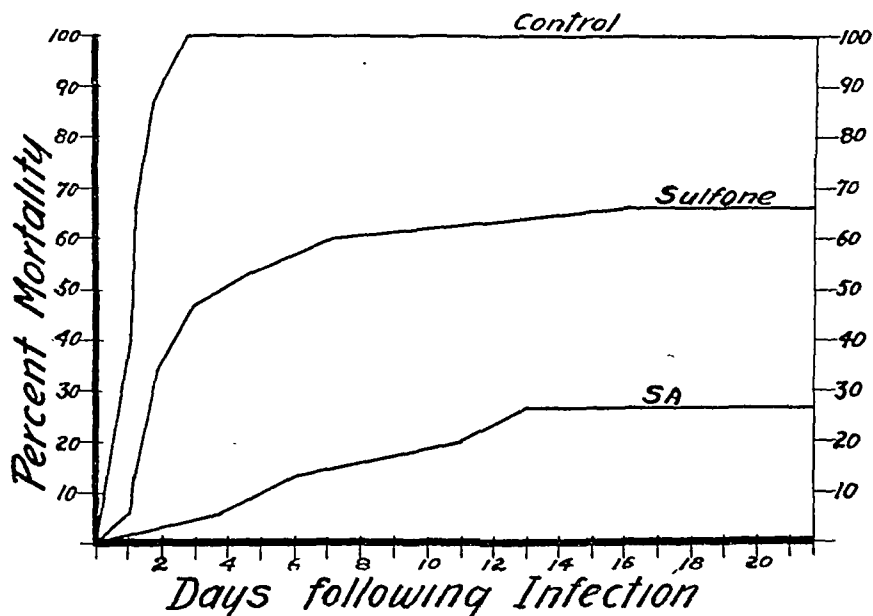


FIG. 1.—Mortality rate of rats infected intracranially with Type II pneumococci (10 fatal doses). All rats were infected with 0.1 cc. of an 18-hour broth culture, diluted 10^{-5} , of Type II pneumococcus (Binda strain). All, except control animals, were treated 6 hours following infection, then twice daily for 2 days, and subsequently once daily for 8 more days. Dose at each treatment was 100 mg. by mouth. Control group consisted of 20 rats; sulphone group 15 rats; SA (sulphanilamide) group 15 rats. All surviving animals were sacrificed on the 22d day.

Results. The results are shown graphically in Figure 2. All controls were dead within 68 hours and all but 1 of the sulphone-treated rats within 44 hours. This animal survived to the end of the experiment. The sulphanilamide group on the other hand showed a 46.7% survival rate with an average survival time of 133 hours for the fatalities.

All blood and spinal cord cultures of the control group were positive. Among the fatalities of the sulphone group there were 1 negative blood and 1 negative spinal cord culture, while from the sulphanilamide-treated fatalities 3 negative blood and 4 negative spinal cord cultures were obtained. All survivors, 7 in the sulphanilamide group and 1 in the sulphone group, gave negative blood and spinal cord cultures.

3. **Experiment With a Moderate Infecting Dose and a 12-hour Delay in the Initial Treatment.** A group of 14 rats were inoculated with about 10 fatal doses as in the first experiment. Seven of the rats were not treated and served as controls, while the other animals were given initial treatments 12 hours after the infection. These treatments consisted of 100 mg. of sulphanilamide by mouth twice daily for 5 days and then once daily for 9 more days. The survivors were sacrificed after 4 weeks.

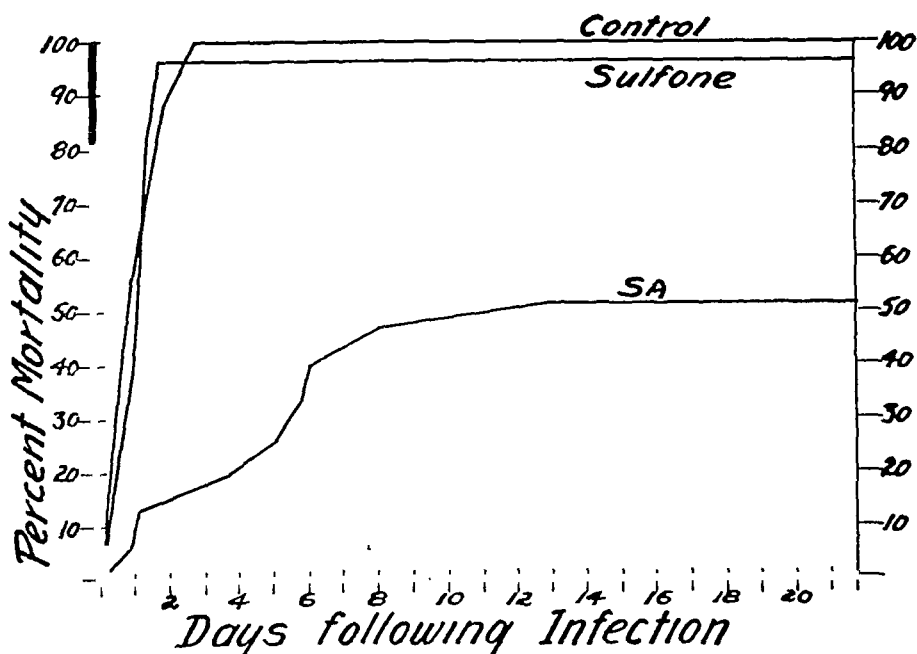


FIG. 2.—Mortality rate of rats infected intracranially with Type II pneumococci (100 fatal doses). All rats were infected with 0.1 cc. of an 18-hour broth culture, diluted 10^{-4} , of Type II pneumococcus (Binda strain). All, except control animals, were treated 6 hours following infection, then twice daily for 2 days, and subsequently once daily for 8 more days. Dose at each treatment was 100 mg. by mouth. Each group consisted of 15 rats. All surviving animals were sacrificed on the 22d day. SA—sulphanilamide.

Results. All untreated rats died within 123 hours (Fig. 3) with an average survival time of 60 hours, while only 3 of the 7 treated animals died (43%), and these with an average survival period of 9.4 days. The last fatality in the treated group occurred on the 19th day. This animal, which had a negative spinal cord but a positive blood culture, died of exsanguination from a ruptured, septic, enlarged spleen.

Symptomatology. The symptoms displayed by the infected rats were variable. While many of the animals merely became weak, lay on one side, and refused to feed until death supervened, others showed incoördination, athetoid movements of the head, loss of equilibrium, and marked irritability. Several rats developed con-

vulsions, a few squealed, and several others, when touched, began biting cage mates indiscriminately. Many of the rats developed wet or crusted noses and crusting about the eyes, giving to the latter a mascara-like effect. Although many of the rats exhibiting convulsions, ataxia, and other disturbances died, there were some that recovered under treatment.

Pathologic Studies. Grossly, only occasional animals showed slight subpial ecchymosis in the region of the inoculation. The purulent nature of the meninges was not discernible macroscopically.

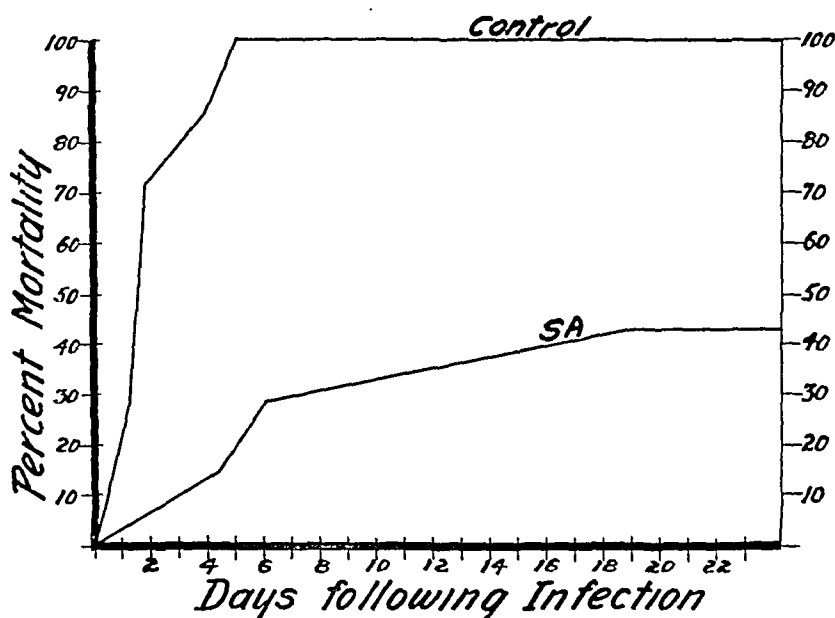


FIG. 3.—Mortality rate of rats infected intracranially with Type II pneumococci (10 fatal doses). All rats were infected with 0.1 cc. of an 18-hour broth culture, diluted 10^{-4} , of Type II pneumococcus (Binda strain). Control group of 7 rats were untreated. SA (sulphanilamide) group of 7 rats were treated 12 hours following infection, then twice daily for 5 days, and subsequently once daily for 9 more days. Dose at each treatment was 100 mg. by mouth. Survivors were sacrificed after 4 weeks.

Microscopically, within 3 hours after infection there were a few foci in various regions of the brain characterized by subpial infiltration of some neutrophils, a few monocytes, and red blood cells. Similar but smaller foci were found at various levels of the spinal cord. Sections from 2 rats killed 5 hours after infection showed no further progress of the inflammation.

Within less than 20 hours 6 control and 3 sulphone-treated rats had died and these, as well as others subsequently, showed extensive and diffuse, although not a uniformly distributed purulent leptomeningitis of the brain (Fig. 4) and spinal cord (Fig. 5). In some animals, the subpial cortex also showed leukocytic infiltration with associated degeneration and necrosis of the brain tissue.

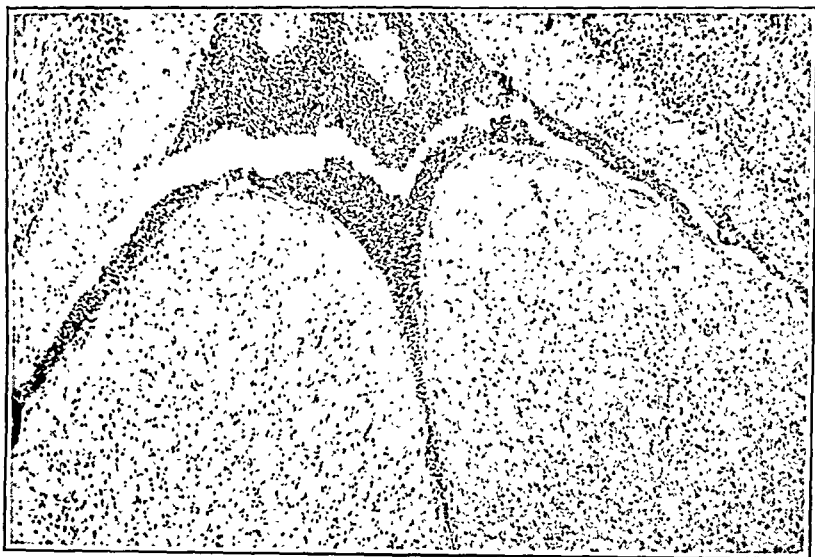


FIG. 4.—Meningitis of brain showing extension of purulent exudate deep into the sulci. Control rat dead in 26 hours. (H. and E. $\times 57$.)



FIG. 5.—Spinal cord showing the purulent meningitis and purulent infiltration of cord substance. Control rat dead in less than 44 hours. (H. and E. $\times 70$.)

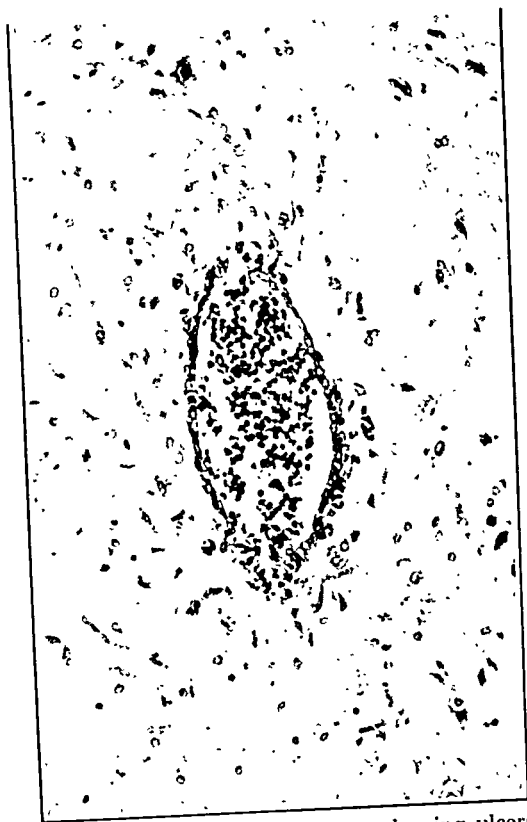


FIG. 6.—Central canal of cord, filled with pus, showing ulceration of ependyma and beginning infiltration of adjoining cord substance. Sulphone-treated rat dead in 29 hours. (H. and E. $\times 170$.)



FIG. 7.—Cortex showing large focus of meningeal calcification with gliosis of underlying cortex and a collection of hemosiderin containing phagocytes. Sulphanilamide-treated rat sacrificed 4 weeks after infection. (H. and E. $\times 140$.)

Chemotherapy resulted in significant differences in incidence and severity of lesions which are summarized in Table 1. About 67.5%

TABLE 1.—INCIDENCE AND SEVERITY OF LESIONS FOUND IN THE DIFFERENT INFECTED GROUPS.*

Type of lesion.	Control groups.		Sulphone-treated groups.		Sulphanilamide-treated groups.	
	No. animals.	%	No. animals.	%	No. animals.	%
Meningitis of brain, slight involvement	6	16.2	16	53.3	31	83.7
Meningitis of brain moderate to severe involvement	29	78.3	12	40.0	1	2.7
Pus in cerebral ventricles	25	67.5	16	53.3	2	5.4
Encephalitis	21	56.7	15	50.0	5	16.7
Spinal meningitis slight involvement	8	21.6	3	10.0	5	13.5
Spinal meningitis moderate to severe involvement	25	67.5	9	30.0	0	0.0
Pus in central canal of spinal cord	17	45.9	5	16.7	0	0.0
Myelitis	16	43.2	12	40.0	1	2.7
Death	37	100.0	23	76.7	15	40.5

* These groups represent animals combined from the various experiments.

of the untreated, 53.3% of the sulphone-treated, and 5.4% of the sulphanilamide-treated rats showed pus in the cerebral ventricles, frequently associated with focal ulceration of the ependymal lining and extension of the leukocytic infiltration into the adjoining brain tissue. A few control as well as treated animals exhibited multiple small cerebral abscesses. The leukocytic infiltration of the brain substance was commonly associated with multiple small and larger hemorrhages.

Pus in the central canal (Fig. 6), often associated with purulent myelitis (Fig. 5), was present in 45.9% of the untreated, 16.7% of the sulphone-treated, and none of the sulphanilamide-treated animals. Rats that died 5 or more days following the infection, or those that were sacrificed at the conclusion of the experiments, showed in the pia a scanty but focally often more abundant monocytic infiltration associated with slight thickening and basophilia of the pia, as well as swelling and proliferation of the pial cells. Indications of healed or healing more destructive lesions were found in some of the recovered animals.* These consisted of large calcium deposits in the meninges (Fig. 7) as well as in the brain tissue, and hemosiderin deposits in the subpial cortex as well as in the paraventricular regions. Indications of a previously existing meningitis could be found in only a few of the spinal cords which showed a scanty monocytic infiltration about some of the larger pial vessels.

Discussion. Although smears, cultures and sections of the spinal cords demonstrated the existence of pneumococcic meningitis at

* A more detailed study of these lesions will be reported elsewhere.

least 3 hours prior to treatment, it is probable that therapy arrested the disease before it reached the proportions usually encountered in man. Nevertheless, all the recovered rats showed evidence of meningitis and some showed more deeply seated lesions (scars, hemosiderin and calcium deposits), which were healed or healing.

Therapy with 4,4'-di-(acetylamino)-diphenylsulphone proved inferior to that with sulphanilamide. This is in agreement with similar findings previously reported by us.^{6b} The fatality rate of the sulphone-treated animals was almost double that of the combined sulphanilamide-treated groups (Table 1). Similarly, the incidence and severity of lesions in the sulphanilamide-treated groups (fatalities as well as survivals) was fractional compared with those of the control or sulphone-treated groups.

The Type II pneumococcus was chosen for these experiments in order to dispel the mistaken notion that only Type III pneumococcic infections are susceptible to sulphanilamide therapy. It should be borne in mind, however, that although sulphanilamide therapy has been proven effective in experimental pneumococcic pneumonia,^{5a,b,8a} clinical corroboration is as yet very incomplete. On the other hand, it has been demonstrated experimentally by us,^{6b} as well as by Branham and Rosenthal² that sulphanilamide and antipneumococcic serum act synergistically. In addition, more recent work^{8c} with Type I pneumococcic meningitis of rats has shown that a new concentrated antipneumococcic rabbit serum* gave results superior to those obtained with sulphanilamide, and that both together gave better results than either alone.

It therefore appears probable that sulphanilamide administered as an adjuvant to serum therapy or alone when the appropriate antipneumococcic serum is not available, may play an important rôle in lowering the mortality rate of pneumococcic pneumonia and meningitis in man.

Conclusions. 1. A cerebrospinal meningitis has been produced in rats with a Type II pneumococcus.

2. Sulphanilamide therapy of this disease effected a marked reduction in mortality as well as in incidence and severity of the lesions.

3. Therapy with 4,4'-di-(acetylamino)-diphenylsulphone was less effective against this infection than sulphanilamide.

4. Sulphanilamide is suggested as an adjuvant to specific serum therapy, or as the primary therapeutic agent when such serum is not available, as a means toward an effectively lowered mortality rate of pneumococcic pneumonia and meningitis in man.

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LYMPHOCYTIC CHORIOMENINGITIS.

REPORT OF A FATAL CASE WITH AUTOPSY FINDINGS.

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DURING the past several years there has come to be recognized a clinical entity which has been labelled under various headings: acute aseptic meningitis,¹¹ lymphocytic meningitis,⁶ acute lymphocytic choriomeningitis¹ and benign lymphocytic meningitis.⁴ With the exception of the fatal case reported by Viets and Warren¹⁰ and the case which developed an obliterative arachnoiditis of the spinal cord, reported by Barker and Ford,³ all cases reported in the literature have run a benign course, a few more protracted than others. The clinical picture has become established, and a responsible virus has been identified by Rivers and Scott⁹ and by Findlay, Alcock and Stern.⁵ Antibodies have been demonstrated by Armstrong and Dickens.¹ However, as 11% of cases whose serum was examined by Armstrong and Wooley² for the presence of protective antibodies gave positive results without recognizable disease of the central

nervous system, the question arises whether or not the clinical entity of "aseptic meningitis" is made up of more than one etiologic entity. Tuberculosis, encephalitis and non-paralytic poliomyelitis in certain respects simulate the clinical findings. A case diagnosed on clinical grounds as benign lymphocytic meningitis by Viets and Warren¹⁰ at necropsy showed evidence of encephalitis. It is the purpose of this paper to report another fatal case with necropsy findings, whose clinical course was that of lymphocytic choriomeningitis.

Case Report.—G. T. M., white male, aged 14 was admitted to the service of Dr. O. H. P. Pepper in the University Hospital on February 4, 1938, and died on February 24, 1938. Ten days prior to admission a dull frontal headache associated with sneezing developed. The next day there was photophobia, anorexia, weakness and listlessness. On the third day, a severe shaking chill was experienced; on the fourth, sudden nausea with repeated bouts of forceful vomiting. Headache disappeared on the seventh day and it was noted that the patient appeared warm, flushed and perspired freely. The 5 days prior to admission were spent in bed chiefly in one position; this consisted of lying on the side with thighs flexed, neck rigid, head extended backwards, pain resulting on attempting to bring the chin forward. He was admitted on the tenth day of the disease, vomiting everything ingested, including fluids taken in an attempt to allay a severe thirst. Past medical history was negative except for whooping cough at 7, chicken pox at 8 and measles at 12 years of age. Family history contained no known tuberculosis.

Physical Examination.—On admission the boy was oriented, quiet, apathetic and drowsy. Temperature was 101, pulse 120 and respiration rate 20 per minute, blood pressure 120/70 (r). There was cervical rigidity, positive Brudzinski's and Kernig's signs and bilaterally equally hypoactive biceps, triceps, Achilles and patellar reflexes. Eyes and eyegrounds were negative except for slightly blurred disc margins. Abdominal reflexes were active. There was no Babinski, Gordon, or Hoffman sign, patellar nor

LEGENDS FOR FIGS. 1 TO 6.

FIG. 1.—The meningeal reaction over the cortex is characterized by thickening due to heavy connective tissue proliferation. There is only a sparse scattering of inflammatory cells within the meshes. Note that the infiltrations are heavier in the sulci. The vessels are dilated with blood. (H. and E., $\times 30$.)

FIG. 2.—The basal meninges show a far greater degree of infiltration with conglomerate masses of lymphocytes. The subarachnoid spaces are obliterated by the inflammatory and fibroblastic proliferation. (H. and E., $\times 100$.)

FIG. 3.—Portion of the wall of the lateral ventricle, showing complete stripping and fragmentation of the ependymal lining. The lymphocytic perivascular infiltration noted in the subependymal zone is confined to this area. The glial proliferation forms small irregular nodules which project into the ventricle. These are seen at the left of the illustration. (H. and E., $\times 40$.)

FIG. 4.—Portions of the choroid plexus are destroyed and replaced by masses of inflammatory exudate consisting of lymphocytes, red blood cells, desquamated choroidal epithelium and fibrin. Other parts of the plexus though relatively preserved show fragmentation of the epithelial cells. (H. and E., $\times 30$.)

FIG. 5.—The ependyma of the floor of the fourth ventricle is entirely denuded and the ventricular floor is frayed and fragmented. The perivascular infiltration is still confined to the subependymal zone. The cells in the subependymal area are largely swollen astrocytes. (H. and E., $\times 100$.)

FIG. 6.—Section through basal ganglia and lateral ventricles disclose no evidence of demyelination (Pal-Weigert stain).

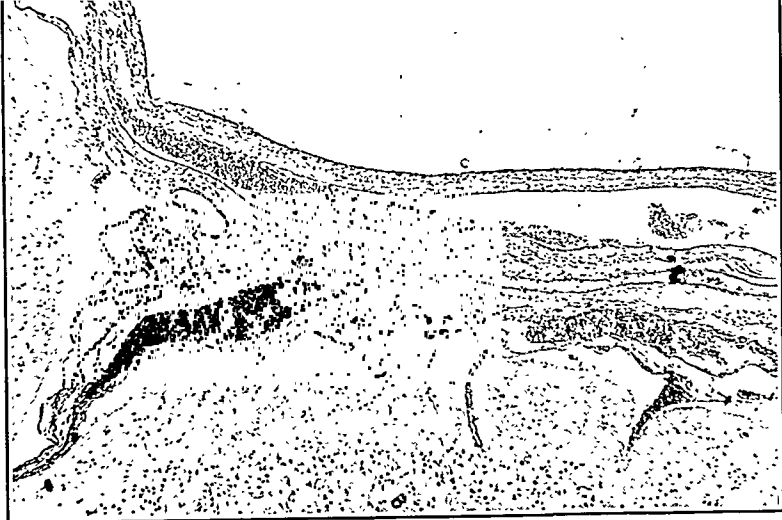


FIG. 1



FIG. 2

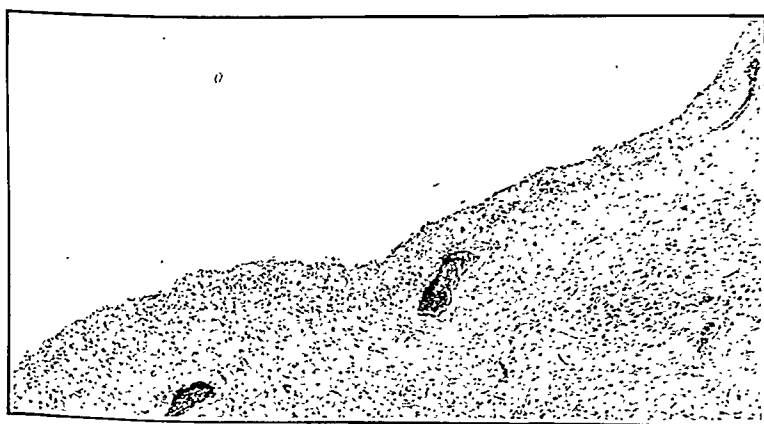


FIG. 3



FIG. 4

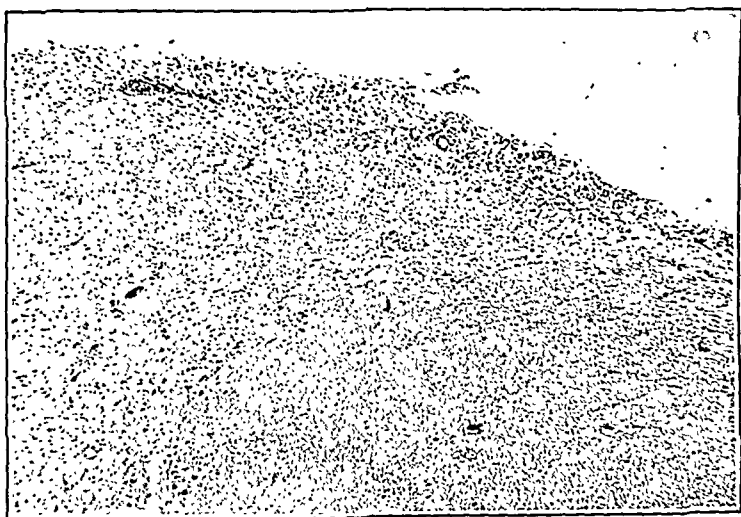


FIG. 5



FIG. 6

ankle clonus. There was no paralysis and speech was normal. The rest of the examination was negative except for a warm, dry skin, heavily coated tongue, engorged mucosa of the turbinates anteriorly, soft blowing systolic basal murmur, tense but not tender abdominal wall.

Laboratory Data.—The white corpuscles numbered 9360, 79% of which were neutrophils. Lumbar puncture performed $\frac{1}{2}$ hour after admission revealed a cloudy fluid, a pressure of 120 mm. of water, 556 cells per c.mm., all of which were lymphocytes (Table 1). Smears for pathogenic bacteria by Gram's method and Ziehl-Neelsen's for acidfast bacilli were negative. Cultures on routine media and on special media for tubercle bacilli were negative. The Kolmer complement fixation test was negative; the colloidal gold curve was 0000111100. For the chemistry of the fluid and characteristics of fluids obtained on subsequent taps see Table 1. Blood Kolmer and Kahn tests and blood cultures were negative. Two guinea pigs were inoculated with 1 cc. of sediment from the fluid, 1 pig received the injection subcutaneously in the groin, the second intraperitoneally. Both pigs died on the 16th day after inoculation; no evidence of tuberculosis was found at necropsy. Congestion of the pigs' lungs was evident and the spleen was slightly enlarged and bloody. The lungs and spleen were ground in salt solution filtered and reinjected into a single pig intraperitoneally. This pig died on the 17th day after inoculation; the organs showed the same gross pathologic picture as outlined above. There was no evidence of virus infection among the guinea pigs nor were there any deaths of a similar nature among other guinea pigs injected.

TABLE 1.—SPINAL FLUID STUDIES.

Date. (1938.)	Day of disease.	Initial pressure in mm. H ₂ O.	Color of fluid.	Cells.	Percent- age lym- phocytes.	Protein in mg. %	Sugar in mg. %	Chlorides in Milli- equiv. per liter
2- 4	10	120	Cloudy	556	100	129	49	103
2- 5	11	150	Cloudy	425	100	227		
2- 6	12	140	Cloudy	830	...	297	64	108
2- 7	13	160	Cloudy	910	85	440	45	112
2- 8	14	250	Yellow	710	90	400	59	111.7
2-10	16	220	Yellow	975	90	520	53	111.9
2-15	21	120	Yellow	475	90	401		
2-22	28	90	Yellow	217	100	367		
2-24	30	0	..	63	100	245		

2- 4 Culture and Wassermann test negative. Colloidal gold: 0000111100.

2- 7 No pellicle. Culture for Tb. negative. Guinea pig inoculation for Tb. negative.

2-22 Queckenstedt test negative.

2-24 Queckenstedt test positive. Evidence of block by spinal and cisternal puncture. Rise in spinal pressure of 12 mm. on abdominal straining.

Course in Hospital. In the hospital the boy improved subjectively and objectively, so that by the 6th day after admission (15th day of the disease) temperature was normal, he was more alert, appetite had improved and vomiting and headache had disappeared. Cervical rigidity had markedly decreased but did not disappear. Spinal fluid examinations as in Table 1. On the 21st day of the disease he vomited twice; examination of the eye-grounds showed no detectable changes and spinal fluid pressure was normal. A chest Roentgen ray revealed no evidence of pulmonary tuberculosis. On the 28th day of the disease he developed nausea and vomiting and complained of marked vertigo when he moved his head. Physical examination at this time disclosed a coarse lateral and upward nystagmus and no other findings. The new symptoms were interpreted as being due to an inflammatory invasion or reaction of the membranous labyrinth. There was no

febrile response. The next day the symptoms continued despite the intravenous administration of ammonium chloride in 5% glucose in an attempt to replace sodium ions. On the 29th day his pulse which was averaging about 76 dropped to 52 per minute. Nausea and vertigo persisted and he began to complain of severe headache. Eyegrounds showed the discs to be as before. A lumbar puncture was done in the morning and pressure was zero, the Queckenstedt test was positive. A cisternal tap was done in the afternoon, the pressure again was zero, air was injected with the idea of breaking up adhesions; this procedure was followed by relief from headache and vertigo but no objective improvement, the bradycardia persisting. The next afternoon respiration suddenly ceased and did not resume despite artificial and chemical stimulation and the use of a respirator. The pulse gradually becoming weaker until it faded away.

Necropsy. (17 hours after death.) All organs were examined and with exception of the brain, disclosed no evidence of disease grossly or microscopically. No evidence of tuberculosis was found. The brain weighed 1290 gm. Of the central nervous system, only the brain and upper spinal cord were available for study.

Gross Description of the Brain. The brain (fixed in 10% formalin), showed nothing remarkable in the general appearance of the cortex. The meninges appeared somewhat thickened and this was most noticeable at the base and around the brain stem.

The brain was sectioned coronally. The entire ventricular system was dilated to about twice normal size. There were numerous punctate hemorrhages scattered thickly in the periventricular zones. There were also a few noticeable in the ependyma of the lateral ventricles. The choroid plexuses of the lateral third and fourth ventricles appeared discolored and "beefy." There was a distinct impression of the foraminal ring on the cerebellar tonsils.

Microscopic Anatomy. Routine sections were taken from the frontal, parietal and occipital lobes, the basal ganglia, mid-brain, pons, medulla and upper cervical cord. Paraffin, celloidin and frozen sections were prepared. These were stained with Hematoxylin and Eosin, Hematoxylin and Phloxin, Weil's modification of the Pal-Weigert, Globus's modification of Cajal's gold sublimate technique, Scharlach R and Giemsa and Azure II for inclusion bodies.

Meninges. The meninges over the cortex showed a marked degree of thickening due to fibroblastic proliferation (Fig. 1). Small lymphocytes were scattered thinly through the interstices of the heavy strands of connective tissue. In the sulci the infiltration of inflammatory cells was much heavier. The pial vessels were distended and many of them had ruptured. The fact that numerous macrophages contained blood pigment indicates that these extravasations occurred during life.

The character of the meningeal reaction was different at the base and surrounding the brain stem and cerebellum from that on the cortex (Fig. 2). In these sites the inflammatory reaction was more intense. The meningeal spaces were occupied by thick masses of lymphocytes, polyblastic cells, fibrin and fibroblasts. The marked proliferation of connective tissue cells and their tendency to organization suggests that the reaction was of some duration. In many areas the subarachnoid spaces were obliterated by the masses of organizing exudate. The connective tissue response seemed disproportionate to the inflammatory infiltration. Neutrophils were not seen, neither were plasma cells. There was also much hemorrhage in the leptomeningeal spaces and many macrophages contained pigment.

Cortex. A number of sections of various portions of the cerebral cortex were examined and in general they showed strikingly little. There was a mild degree of pericellular and perivascular edema but these changes may

well have been due to fixation. The ganglion cells for the most part appeared entirely normal. There was a mild diffuse increase in the glial nuclei throughout the cortex and subcortex but this again did not appear striking. The vessels were normal and a thorough search failed to disclose any with perivascular infiltrations. The myelin sheath stains failed to show any evidence of myelin damage in either the cortex or subcortex. No inclusion bodies were found in the ganglion cells.

Basal Ganglia and Ventricles. Blocks were taken through the basal ganglia, lateral and third ventricles. The most obvious and remarkable changes were noted in the ventricular walls. Except for small scattered areas, the ependymal lining of the ventricles was entirely denuded and fragmented (Fig. 3). This was true of the entire ventricular system including the aqueduct and fourth ventricle. Throughout the entire ventricular system the subependymal zone was the site of an intense inflammatory reaction. The subependymal vessels were widely dilated with blood and surrounded by thick cuffs of lymphocytes. The tissue for a depth of 1 to 2 mm. was spongy, pale, frayed and occupied by dense accumulations of swollen glial nuclei. These were for the most part astrocytic, but there was a liberal sprinkling of oligodendroglial cells. Throughout this zone there was also a thin sprinkling of lymphocytes which had apparently wandered out into the tissues from the perivascular spaces. Here and there dense nodules of glial nuclei were noted. With Cajal's gold sublimate method a thick felt-work of glial fibers could be demonstrated in the subependymal zones. The absence of fat with the Scharlach R stain indicated that the inflammatory process was productive rather than necrotizing. At many points in the ventricular walls the dense accumulations of glial cells and fibers formed small microscopic nodules projecting into the ventricles, a so-called "granular ependymitis." These ependymal granulations were scattered throughout the walls of the entire ventricular system. None was seen in the aqueduct large enough to cause obstruction. The presence of this type of ependymitis also indicates that the inflammation was subacute. The septum pellucidum was studded with perivascular infiltrations, distended veins and perivascular hemorrhages. The most interesting observation was the sharp limitation of the inflammation to the area subjacent to the ependyma.

Of all parts of the brain examined, the choroid plexuses of the lateral ventricles showed the greatest degree of inflammatory response. The choroidal vessels were widely dilated and there were numerous hemorrhages within the papillæ. The epithelial cells were swollen and many of the tufts were fragmented and necrotic. In certain areas the structure of the plexus was no longer recognizable and all that one could see was a nodular conglomerate of inflammatory cells, macrophages, red blood cells, fibrin and necrotic epithelial cells (Fig. 4).

Again in the subependymal zone beneath the attachment of the choroid plexus to the wall of the ventricle the inflammatory reaction was very intense, the tissue was pale and edematous and lymphocytes were diffusely scattered through the interstices along with numerous glial cells.

Unfortunately, the choroid plexuses of the third and fourth ventricles were not included in the available sections, so that one can not state what they showed; but it is probable that similar findings existed. Aside from the changes described subjacent to the ependyma, the basal ganglia were essentially normal. The ganglion cells of the thalami and lenticular nuclei showed no degenerative changes. In those portions near the subependymal strip there was a definite increase in the glia but further away there was no significant glial reaction. A search through the basal ganglia failed to disclose any perivascular infiltrations. Myelin sheath stains showed no evidence of demyelination in either the basal ganglia or the internal capsule (Fig. 6). No pathologic changes were noted in the optic nerves.

Midbrain. The ependyma of the aqueduct showed essentially the same changes as were seen in the lateral ventricles. It was stripped and fragmented, the area subjacent was spongy and filled with swollen glial nuclei and lymphocytes. There were large perivascular infiltrations. The ganglion cells of the periaqueductal gray matter were swollen, the Nissl substance was disintegrated and the nuclei were eccentrically placed. The cells of the trochlear and oculomotor nuclei also showed degenerative changes of the same nature. There was a marked increase in the astrocytic glia in the periaqueductal gray substance, and inflammatory cuffs about the vessels. Cells in the deeper nuclei of the reticular substance were normal and myelin stains showed no injury of the tracts and fibers of the midbrain. No inclusion bodies were found in this region.

Pons. The walls, roof and floor of the upper part of the fourth ventricle showed the same pathologic alterations noted in the other portions of the ventricular system. There were numerous ependymal granulations on the floor and walls with the same characteristics as those described in the lateral ventricles. The tegmentum and basilar portions of the pons were altogether normal.

Medulla. The section through the medulla passed through the level of the superior olives. The inflammatory reaction in the floor of the fourth ventricle was very severe. The ventricular floor, as well as the ependyma, was disintegrated to a depth of about 1 mm. The tissue was packed with lymphocytes and large ameboid glial cells. This was the only area where the reaction was severe enough to cause inflammatory softening. The region of the acoustic tubercles on both sides and the medial vestibular nucleus on the left were necrotic and filled with "gitter" cells, proliferated and degenerated astrocytes, tissue fragments and lymphocytes. The vessels in these regions were surrounded with wide perivascular cuffs and the veins were engorged with blood. The ganglion cells of the *substantia grisea reticularis* were shrunken and pyknotic. The nerve cells of the superior olives showed degenerative changes. In spite of these ganglion cell alterations in the deeper portions of the medulla there were no perivascular infiltrations except in the subependymal zone and the area of infiltration was sharply limited to the region of the ventricle. The evidences of injury to the deeper gray masses point to the penetration at least of toxic substances. In general, the inflammatory reaction seemed to extend deeper beneath the ependyma of the fourth ventricle than elsewhere in the ventricular system (Fig. 5).

Cerebellum. The nuclei of the cerebellum were entirely normal. This was also true of the cortex and subcortex of the cerebellum. No perivascular infiltrations were found in this structure.

The ependyma of the central canal was present and intact. The ganglion cells of the anterior horns were entirely normal. There was no evidence of demyelination. The meninges surrounding the cord were thickened and were sparsely infiltrated with lymphocytes. There were also small extravasations of blood from the distended veins.

Pathologic Summary. In brief, the essential pathologic findings consisted of a marked thickening of the meninges due to connective tissue proliferations with obliteration of the subarachnoid spaces. The meninges were infiltrated with lymphocytes, red blood cells and macrophages. The cortex, basal ganglia and subcortical white matter were on the whole unaffected. The ependyma of the entire ventricular system was denuded and fragmented and a narrow subependymal zone was the site of an intense inflammatory reaction characterized by perivascular lymphocytic infiltrations, glial proliferations, engorgement of the vessels and hemorrhages. The walls of the ventricles were studded with ependymal granulations. The choroid plexuses were partly necrotic and heavily infiltrated with inflammatory exudate. In the floor of the fourth ventricle the process was severe enough to cause softening especially involving the acoustic tubercles and

the right medial vestibular nucleus. The disease was unusual in that while the meninges, ventricular walls and choroid plexuses showed an intense inflammatory reaction, the remainder of the brain substance showed none at all and was essentially normal.

Pathological Comment.—The cause of death in this patient appears to have been due to increased intracranial pressure, a result of block caused by inflammatory obliteration of the subarachnoid fluid spaces. This is suggested by the fact that death was sudden and that it coincided with the finding of block by lumbar and cisternal puncture. This impression is substantiated by the presence of dilated ventricles, clear evidence of a preëxisting interference with the C.S.F. circulation and by the presence of a pressure cone. The correlation of the patient's symptoms with the pathologic findings in the brain presents some difficulties. His outstanding complaint toward the end of his illness was intense vertigo, nausea and nystagmus produced by movements of the head. This had been interpreted as possibly due to a perilabyrinthitis. In view of the marked inflammation associated with inflammatory softening in the floor and lateral recesses of the fourth ventricle it seems that the patient probably had a so-called Bruns syndrome due to injury of the vestibular nuclei. Since the brain itself does not present changes adequate to cause death, it is likely that had block not supervened, the patient would have recovered.

Discussion. Although in the case described here, no attempts were made to identify the virus, the diagnosis of lymphocytic choriomeningitis was made on clinical grounds. Tuberculosis was ruled out by examination of spinal fluid by smear, culture, guinea pig inoculation and necropsy findings. Syphilis was excluded on basis of serologic tests upon blood and spinal fluid. The lack of any evidence of intraparenchymal disease of the central nervous system and the presence of an almost pure meningeal picture tended to exclude encephalitis. The high mononuclear content of the spinal fluid argued against non-paralytic poliomyelitis; further exclusion was made on necropsy findings, there being almost a complete absence of disease of the motor nuclei.

Further evidence that our case falls into the group called lymphocytic choriomeningitis is had in the resemblance of the necropsy findings to those reported in experimental monkeys by Lillie.⁷ In his series of monkeys, the meninges showed slight to moderate focal to diffuse lymphocytic infiltration most marked in the sulci and fissures. The choroid plexuses showed at least a focal lymphocytic infiltration, often they were swollen and densely infiltrated with lymphocytes, serous exudates, macrophages and plasma cells. There was desquamation of the ependyma from the walls and plexuses in a number of animals. In a few animals subependymal edema and focal infiltration with lymphocytes were found. An explanation of

why this virus attacks the choroid plexus and ependyma cannot be made.

Contrasting the necropsy findings in our case with those reported by Viets and Warren,¹⁰ differences are found insofar as Viets' and Warren's case showed evidence of encephalitis; in our case, the perivascular inflammatory reaction was sharply limited to the subependymal zones.

An interesting similarity between our case and that reported by Barker and Ford³ is that in which a patient had an episode diagnosed as lymphocytic meningitis; the virus was identified by Rivers and Scott. Four months after the acute episode she developed evidences of severe arachnoiditis which caused obliteration of the spinal subarachnoid space. When Dandy explored the lower thoracic cord, a thick fibrous mass was found below the dura, completely obliterating the subarachnoid space in the region examined. A basal arachnoiditis was found in our patient which had caused a blockage of the cerebro-spinal fluid exit and gave rise to distention of the ventricular system resulting in respiratory failure.

Of course the absence of virus studies prevents absolute knowledge of the nature of the case; but the clinical picture, similarity of pathologic findings with those found in experimental monkeys and the death of two guinea pigs following inoculation with spinal fluid with no evidence of tuberculosis and at a time when there was no evidence of any virus infection among guinea pigs, made us believe that our case falls into the group labelled acute lymphocytic choriomeningitis. A case referred to by Lucchesi⁸ was found to have evidence of poliomyelitis at necropsy.

As time goes on and more fatal cases are reported, it may be found that the disease has its specific fatal characteristics and in view of this, the term "benign" may no longer be appended. We had expected to find evidences of encephalitis at necropsy, but found none.

Summary. The clinical course, laboratory and necropsy findings of a patient believed to be suffering from lymphocytic choriomeningitis is presented. The chief changes in the brain (see pathological summary) were found in the ventricular walls, choroid plexuses and the basal meninges. No inclusion bodies were found. Death was due to respiratory failure secondary to increased intracranial pressure as the result of blockage of subarachnoid spaces at the base of the brain.

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TOXICOLOGY OF FLUORIDES.

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1. Methods for the Detection of Fluorine in Human Tissues.*

Many qualitative tests have been devised for the detection of fluorine. The outstanding ones are: the spectrographic test,⁴⁹ the Lanthanum fluoride precipitation,⁴⁶ the silico-molybdic acid test,^{16,19} the bleaching of the zirconium-alizarin lake,¹⁵ the zirconium oxy-chloride purpurin,³⁷ or the zirconium quinalizarin,⁶⁰ the zirconium salt of para-dimethyl amino-azo-phenyl arsenic acid spot test,²⁰ the etch test,¹¹ the precipitation of silicic acid from the volatilized silicon fluoride in the hanging drop,^{41b} the sodium fluosilicate crystal test,⁷ and the barium fluosilicate crystal test.⁷ We have applied all these methods to the detection of fluorine in human tissues, and have found that most of them are not sensitive enough, since the fluorine content in the organs of a fatal poisoning is very often as little as 40 γ in 10 gm. of tissue. Although it has been stated¹¹ that by proper technique the etch test can be made quite sensitive, our investigations have shown that although it is sensitive enough for the detection of fluorine in the gastro-intestinal tract in cases of acute fluorine poisonings, because the fluorine content is relatively large, it is not sensitive enough for the detection of fluorine in blood and in the internal organs. Most of the above methods are not specific tests for fluorine: phosphates, sulphates, iron, and other substances, which may pass over with the fluorine in the form of a spray during the distillation of the fluorine, give the same reactions as does the fluorine.

2. Technique Best Adapted for the Detection of Fluorine in Tissues.

In the toxicologic examination of a suspected case of poisoning by fluorine it is necessary to detect the fluorine, not only in the gastro-intestinal tract, but also in the internal organs. The amount of

* The term "fluorine" used throughout this paper designates fluoride ions originating from soluble fluorides, fluosilicates, or hydrofluoric acid.

fluorine present in the organs of a fatal fluorine poisoning is relatively small (quite often as little as 40 γ in 10 gm. of tissue).

Formerly, the etch test was applied to the ashed tissues. The method has the disadvantage that it is tedious and time-consuming completely to ash the tissues at the low temperature essential to prevent any volatilization of the alkali fluorides. Then again, since the test is not very sensitive, at least 100 gm. of tissue must be ashed, while 10 gm. or less are sufficient when our modified sodium fluosilicate test (described below) is used.

The primary difficulty in the detection of fluorine in so complex a medium as tissues and blood is the removal of the organic material. The ashing process is slow, and it may result in the loss of much of the fluorine if it is not carefully controlled. For this reason several other methods of preparing the material for analysis were studied in order to develop a quick convenient procedure. The method finally adopted follows:

Ten gm. of the minced tissue are placed in a 100-cc. beaker, an equal volume of water and 3 cc. of concentrated nitric acid are added, and the material is thoroughly mixed. After 3 to 5 minutes, 30 cc. of water are added with constant stirring. The material is then filtered, preferably by means of a Buchner funnel and suction. The filtrate containing the fluorine is transferred to a 100-cc. beaker, 0.5 to 1 gm. of solid lanthanum acetate, and enough solid ammonium acetate is added until the solution is definitely alkaline to methyl orange, whereupon a gelatinous precipitate of lanthanum salts appears. The mixture is boiled for a few minutes in order to coagulate the precipitate. After the precipitate has been allowed to settle, the supernatant liquid is filtered through a small Gooch crucible by aid of suction. The precipitate is finally also transferred to the Gooch by means of a stream of water. Since this gelatinous precipitate filters slowly, the following procedure may be resorted to: After the supernatant fluid has been decanted into the Gooch crucible, the gelatinous precipitate remaining in the beaker is dried, and heated to approximately 150° C. for a few minutes. The sandy residue is boiled up with a few cc. of a dilute acetic acid ammonium acetate mixture, and then filtered through the same Gooch crucible, and washed with a 1% lanthanum acetate solution. The asbestos mat holding the precipitate is transferred to a 5-cc. porcelain crucible, and dried on a hot plate. When cool, a little powdered glass is mixed with the dry material, a few drops of sulphuric acid are added, and the crucible is immediately covered with a microscope slide from the under surface of which is suspended a small drop of 5% NaCl solution. The crucible is placed on a small metal block maintained at a temperature of approximately 150° C. and a small beaker of ice-cold water is placed on the slide in order to retard the evaporation of the suspended drop. If relatively large amounts of fluorine are present the heating can be omitted. After 3 to 5 minutes the slide is removed, and examined under the microscope (high magnification) for 6-pointed stars or slightly pink hexagonal crystals of sodium fluosilicate.

It is not absolutely necessary to use 10 gm. of tissue in this test, for a 5-gm. sample from a case of poisoning by fluorine always yields definite crystals of sodium fluosilicate. One can easily detect as little as 10 γ of fluorine in 5 gm. of tissue by this procedure.

When this test was applied to 50-gm. portions of normal tissue, or normal blood, 3 or 4 crystals of sodium fluosilicate in the entire

field were observed, due to the normal fluorine content. The results on 20-gm. portions of normal tissues and blood were always negative. A positive result, therefore, when 10 gm. or less of tissues are used, always indicates the presence of abnormal amounts of fluorine.

Stomach contents and urines in acute fluorine poisonings contain much larger amounts of fluorine than do the tissues. The method can, therefore, be simplified by using smaller samples and omitting the nitric acid and lanthanum treatment. One gm., or even less, of the material is placed in a 5-cc. crucible. It is made slightly alkaline with sodium hydroxide solution, and dried on a hot plate. A little powdered glass is mixed with the solid material, and enough sulphuric acid is added just to cover the mixture. The crucible is immediately covered with a microscope slide from which is suspended a small drop of 5% NaCl solution. From here on the procedure is the same as described above.

In acute fluorine poisonings, positive results have been obtained in this manner from as little as 1 drop of stomach contents or urine. If large amounts of stomach contents or urine are used, the method given for tissues must be used because of the excessive amount of organic material present.

The test can be used for corroborating the clinical diagnosis of fluorine poisoning, for the procedure is short and simple, and the sensitivity is such that fluorine can be detected in 5 cc. of blood, or 1 cc. of urine in such cases. The test gives a negative result when applied to 5 cc. of blood, or 1 cc. of urine taken from normal individuals.

3. Methods for the Quantitative Determination of Fluorine. All the available quantitative methods for fluorine were studied as to their applicability for the determination of small quantities of fluorine as found in human organs. The gravimetric methods consist in weighing the fluorine as calcium fluoride;^{8,52,69} as lanthanum fluoride;⁴⁶ as potassium fluosilicate;¹² as lead chlorofluoride;⁶⁴ as triphenyl tin fluoride;¹ as silicon tetrafluoride after collecting the latter in an absorption tube; by driving off all of the fluoride as silicon tetrafluoride, and determining the loss in weight of the sample;⁷⁶ by determining the loss in weight of a glass funnel etched by hydrogen fluoride.⁴⁵ In the volumetric procedures, the fluorine in the form of silicon tetrafluoride is distilled into water, and the fluosilicic acid produced is titrated with standard potassium hydroxide solution;⁴⁸ or the fluosilicic acid is treated with potassium chloride, and the hydrochloric acid produced is titrated with standard sodium hydroxide solution;⁵⁰ a solution of the neutral fluoride salt is titrated with standard ferric chloride using potassium thiocyanate as indicator;^{28,70} the neutral fluoride salt is treated with an excess but known quantity of ferric chloride solution, and the excess is determined by adding potassium iodide, and titrating the liberated iodine with standard sodium thiosulphate;^{18,21b} titrating the fluorine with standard cerium nitrate;^{6,32,56} or with standard zirconium

oxychloride solution, using purpurin as indicator;³⁷ titrating the fluorine with standard thorium nitrate solution, using zirconium alizarin lake⁷⁵ or zirconium quinalizarin⁶⁰ or thorium alizarin lake³ as indicators. The colorimetric methods are based on the bleaching action of fluorine ions upon colored substances such as peroxy-titanic acid;^{66,72} ferric thiocyanate;²² ferric acetyl acetone;^{5,74} and various zirconium lakes.^{17,37,53,60}

Our studies as to the application of the various gravimetric, volumetric and colorimetric procedures to the quantitative determination of small amounts of fluorine, in human tissues, has revealed that the thorium nitrate-alizarin volumetric method³ is best adapted from a standpoint of accuracy, sensitivity and simplicity of technique.

4. Technique for the Quantitative Determination of Fluorine in Tissues.

A 50-gm. portion of finely ground tissue in a porcelain or silica dish is thoroughly mixed with 2% of its weight of Na_2CO_3 (20 cc. of 5% solution). After drying on a steam bath, the material is placed into an electric muffle and kept at dull red heat until completely charred, and no more volatile organic vapors are seen coming off. The material must not be allowed to glow. The charred mass is then pulverized, replaced into muffle and ashing continued at dull red heat for 2 to 3 hours. The black ash is then leached, by boiling with 100 to 200 cc. of water. The supernatant liquid is filtered into a 400-cc. beaker. A few cc. of 50% perchloric acid and a little water is added to the residue in order to dissolve any CaF_2 if present. Filtration is completed and the black residue on the filter paper is washed free of any perchloric acid, adding the washings to the main solution in the beaker. To the residue and filter paper is added 0.25 gm. Na_2CO_3 (in solution), well mixed, and dried on steam bath. The ashing of the residue is now completed in muffle at dull red heat, until a grayish-white ash is obtained. The ash is dissolved by adding 5 cc. of 10% perchloric acid and then quantitatively washed into the main solution in the 400-cc. beaker. The mixture thus obtained is made alkaline, to phenolphthalein, with NaOH solution, and then evaporated to 20-cc. volume. It is now quantitatively transferred to a 150-cc. distillation flask, several small glass beads are added, 25 cc. of 60% perchloric acid are slowly introduced and water added to make the total volume between 80 and 100 cc., so that the solution may have a boiling point of about 110°C . Potassium carbonate is slowly added with constant mixing, until a small crystalline precipitate of potassium perchlorate forms. These crystals serve as nuclei for the formation of bubbles of steam which prevent bumping during the distillation. A small amount of freshly prepared Ag_2O is added to prevent the distillation of any chloride (as HCl). The distilling flask is then set up for distillation, resting in a $2\frac{1}{4}$ -inch diameter opening of an asbestos mat. The neck of the flask is fitted with a 2-hole rubber stopper, through which passes a thermometer and a capillary tube, both of which extend into the liquid in the flask. A dropping funnel is connected to the upper part of the capillary tube so that water can be added, gradually, during the distillation. The side arm of the distilling flask is connected with a long water-cooled condenser, and adaptor, the latter dipping into 2 cc. of 1% NaOH solution in a 500-cc. receiving flask. The distillation is then carried on until the boiling point rises to 140°C . It is kept between 135° and 140°C . through the entire distillation, by gradually introducing water through the capillary tube; 250 cc. of the distillate are collected, because our experiments on this point indicated this amount of distillate is required for complete recovery of the fluorine.

The distillate containing the fluorine, while still alkaline, is evaporated to a volume of about 5 cc., then quantitatively transferred to a 30-cc. test tube, and the volume made up to 10 cc. with water. For very small quantities of fluorine (order of 10 γ) the volume is limited to 3 cc. To this solution are now added 10 cc. of ethyl alcohol, 0.03 cc. of a 0.05% aqueous solution of sodium alizarin sulphonate, dilute (1 to 50) HCl dropwise until the transition color (yellow) of the indicator appears, and 1 cc. of a sodium hydroxide-chloroacetic acid buffer (1 gm. NaOH + 4.72 gm. of chloroacetic acid in 100 cc. of solution).*

A blank reference standard is prepared by placing 20 cc. of 50% alcohol into a similar test tube, and adding the same quantity of the alizarin indicator and buffer as above. Standard thorium nitrate solution (0.001 N) is then added from a micro-burette until a faint pink color appears. This pink color is the reference standard.

The fluorine content of the solution prepared above is now titrated by slowly adding 0.001 N or 0.01 N (depending on the amount of fluorine expected to be present) thorium nitrate solution, from a micro-burette, until a faint orange color develops. The titration is then completed by adding a fraction of a drop of the standard solution, per minute, until the solution assumes the same pink color of the blank reference standard previously prepared. The volume of standard thorium nitrate solution required in the preparation of the reference standard is then deducted from the actual titration figure.

Calculation. Since 1 cc. of 0.01 N thorium nitrate solution is equivalent to 190 γ of fluorine, and 1 cc. of 0.001 N to 19 γ , the number of cc. of standard thorium nitrate used, multiplied by the fluorine equivalent, gives the fluorine content of the 50-gm. portion of tissues used for analysis. Somewhat more accurate results are obtained if one determines the fluorine content from the titration figures obtained by titrating a series of known fluorine solutions.

5. The Fluorine Content of Normal Human Tissues. Since fluorine is so widely distributed in Nature, it is not surprising to find it present in normal human tissues. The values reported in the literature vary widely, due no doubt in most cases to the inaccurate methods of analysis employed. Some of the values are given in Table 1.

The presence of much larger amounts of fluorine in the bones and teeth than in soft tissue has been definitely established, but the amounts reported in the literature vary as much as from 0.0%²¹ to 1.55%.⁷⁷ It has also been shown that fluorine accumulates in the bones and teeth when small amounts of fluorine are present in the daily diet.^{10,14,35,51,58,62}

In order definitely to establish the true fluorine content of normal human soft tissues, bones, teeth, blood and urine, a series of analyses were conducted. Both the calcium hydroxide and sodium carbonate methods of ashing were employed. Controls were included to which definitely known amounts of fluorine had been added. The results are recorded in Table 2.

That the material titrated was actually fluorine was confirmed in the case of each tissue as follows: After the titration had been completed, the precipitate of thorium fluoride was centrifuged down.

* Suggested by Hoskins and Ferris³¹ for controlling the pH during the titration.

The supernatant liquid was poured off, and the precipitate was washed into a 5-cc. crucible. A drop of dilute sodium hydroxide was added and the solution was evaporated to dryness. The presence of fluorine in the precipitate was demonstrated by the typical sodium fluosilicate crystal test.

TABLE 1.—FLUORINE CONTENT OF NORMAL HUMAN TISSUES REPORTED BY VARIOUS INVESTIGATORS. (EXPRESSED IN MG. PER 100 GM. TISSUE.)

Blood	0.35	Zdareck.
	0.46	Gautier and Clausmann.
	0.05-0.10	Goldemberg and Schreiber.
	None	Stuber and Lang.
	3.97 (in hemophilia)	Stuber and Lang.
Brain	0.02	Brandes
	0.06-0.07	Zdareck.
	0.71 (adult)	Gautier and Clausmann.
Liver	0.18 (newborn)	Gautier and Clausmann.
	0.21-0.31	Zdareck.
	0.64 (adult)	Gautier and Clausmann.
	0.37 (newborn)	Gautier and Clausmann.
Kidneys	0.45-0.51	Zdareck.
	0.26	Gautier and Clausmann.
Heart	0.16	Zdareck.
Lungs	0.09-0.17	Zdareck.
	0.44	Gautier and Clausmann.
Spleen	0.27-0.62	Zdareck.
Muscles	0.16	Gautier and Clausmann.
Thyroid	0.54	Gautier and Clausmann.
Urine	0.018	Gautier and Clausmann.
	0.03-0.17	Goldemberg and Schreiber.
Feces	0.42	Gautier and Clausmann.
	0.04-0.07	Goldemberg and Schreiber.
	0.04-0.07	Goldemberg and Schreiber.
Bile	0.048	Gautier and Clausmann.
Milk	0.04-0.07	Goldemberg and Schreiber.
Femur	0.29	Zdareck.
Humerus	0.35-0.45	Zdareck.

The data in Table 2 reveal the following interesting points: (a) Very small amounts of fluorine are found in normal human tissues (0.00002 to 0.00008%) (20 to 80 γ in 100 gm.). (b) There seems to be no appreciable accumulation of fluorine in any one of the vital organs. (c) The values reported by previous investigators range from 0.000000 to 0.00397%⁵⁷ (0.000 to 4000 γ in 100 gm.). The present investigation disproves the entire absence of fluorine, as well as the high values and wide variations which have been reported. (d) The fluorine content of teeth and bones is of the order of 0.01 to 0.03%. The actual value undoubtedly varies with the amount of fluorine in the daily diet. (e) The fluorine content of the urine is of the same order of magnitude as that of the tissues. It is to be expected, however, that it would vary with the amount of fluorine in the diet. (f) The results of the control analyses, to which definitely known quantities of fluorine were added, confirm the accuracy of the method.

TABLE 2.—FLUORINE CONTENT OF NORMAL HUMAN TISSUES.

Tissue used for analysis, gm.	Ashing method.	Fluorine added, mg.	Fluorine found, mg.	Fluorine in wet tissue, %.
Liver (1) . . . 50	Ca(OH) ₂	..	0.030	0.000060
50	Na ₂ CO ₃	..	0.035	0.000070
50	Ca(OH) ₂	..	0.030	0.000060
Liver (2) . . . 50	Na ₂ CO ₃	..	0.020	0.000040
50	Na ₂ CO ₃	0.500	0.520	0.000040
50	Ca(OH) ₂	0.100	0.118	0.000036
Liver (3) . . . 100	Ca(OH) ₂	..	0.065	0.000065
100	Ca(OH) ₂	..	0.055	0.000055
Kidney (1) . . . 50	Ca(OH) ₂	..	0.039	0.000078
50	Ca(OH) ₂	..	0.039	0.000078
50	Ca(OH) ₂	0.500	0.535	0.000070
Kidney (2) . . . 50	Ca(OH) ₂	..	0.028	0.000056
50	Na ₂ CO ₃	..	0.030	0.000060
50	Na ₂ CO ₃	0.050	0.080	0.000060
Blood (1) . . . 100	Ca(OH) ₂	..	0.020	0.000020
Blood (2) . . . 50	Na ₂ CO ₃	..	0.010	0.000020
Blood (3) . . . 50	Na ₂ CO ₃	..	0.021	0.000042
Blood (4) . . . 100	Ca(OH) ₂	..	0.064	0.000064
Brain (1) . . . 50	Na ₂ CO ₃	..	0.028	0.000056
Brain (2) . . . 50	Na ₂ CO ₃	0.050	0.084	0.000068
Brain (3) . . . 50	Ca(OH) ₂	0.500	0.525	0.000050
Brain (4) . . . 50	Ca(OH) ₂	0.500	0.520	0.000040
Lung (1) . . . 50	Na ₂ CO ₃	..	0.008	0.000016
Lung (2) . . . 50	Na ₂ CO ₃	..	0.012	0.000024
Lung (3) . . . 100	Na ₂ CO ₃	..	0.042	0.000042
Heart (1) . . . 50	Na ₂ CO ₃	..	0.030	0.000060
Heart (2) . . . 100	Ca(OH) ₂	..	0.044	0.000044
Spleen (1) . . . 50	Na ₂ CO ₃	..	0.015	0.000030
Spleen (2) . . . 100	Ca(OH) ₂	..	0.025	0.000025
Femur (1) . . . 7.80	Direct	..	0.930	0.0119
Femur (2) . . . 4.80	Direct	..	0.535	0.0112
Femur (3) . . . 3.21	Direct	..	0.454	0.0141
Teeth (1) . . . 2.00	Direct	..	0.620	0.0310
Teeth (2) . . . 1.53	Direct	..	0.421	0.0275
Enamel . . . 0.36	Direct	..	0.070	0.0190
Urine (1) . . . 200	Ca(OH) ₂	..	0.080	0.000040
Urine (2) . . . 250	Na ₂ CO ₃	..	0.130	0.000052
Urine (3) . . . 250	Na ₂ CO ₃	..	0.140	0.000056
Urine (4) . . . 250	Na ₂ CO ₃	..	0.120	0.000048

6. The Distribution of Fluorine in the Body Tissues in Fatal Cases of Fluorine Poisoning. The fluorine content of some of the tissues in fatal cases of fluorine poisoning have been reported. Luhrig⁴¹ found 0.00103% in the brain and 0.00214% in the liver of a fatal case of sodium fluosilicate poisoning. In another of his cases the liver contained 0.0015% fluorine.^{41b}

Sharkey and Simpson⁵⁷ found 0.0837% in the liver and 0.0543% in kidney tissue. McNally⁴³ reports the following percentages of fluorine in 3 poisoning cases: Liver, 0.0025 to 0.1142; kidneys, trace to 0.0591; spleen, 0.1065; blood, 0.0654; lungs, 0.0706; heart, 0.0880; pancreas, none.

In Table 3 we have charted our findings on the fluorine content of several organs of 5 fatal acute cases of sodium fluoride poisoning. Cases 2, 4 and 5 were brought to the hospital and died in less than 24 hours. Cases 1 and 3 were found dead.

It is interesting to note that in 2 of our fatal cases the fluorine content of the tissues at the time of death was less than some of the values which have been reported by several investigators for normal tissues. On the other hand, the fluorine content of the organs of these same 2 fatal cases is twice as high as the highest normal fluorine content as determined by our technique. This seems further to corroborate the fact that the normal fluorine content of organs reported in the literature is much too high.

TABLE 3.—FLUORINE CONTENT OF HUMAN TISSUES IN FATAL CASES OF POISONING (VALUES REPORTED IN PER CENT).

Tissue.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.
Blood . . .	0.00155	0.00121	0.00108	0.00042	0.00035
Spleen	0.00118			
Kidney	0.00116	0.00107	0.00046	
Brain	0.00034	0.00016
Heart	0.00106			
Lung . . .	0.00156	0.00124			
Liver . . .	0.00150	0.00122	0.00106	0.00044	0.00044

Since all of the organs and tissues in our fatal cases were not submitted for analysis and since the fluorine distribution in all tissues was desired, a series of experiments was carried out in which dogs were used as subjects.

Sodium fluoride was administered to each of 3 dogs, Dogs 1, 2, 3, and sodium fluosilicate to 2 others, Dogs 4 and 5, either in food or by stomach tube. The symptoms observed were persistent vomiting, salivation and lachrymation, stupor and weakness, muscular twitchings, diarrhea, acceleration and deepening paralysis, terminal clonic convulsions, and early rigor. In all cases the heart beat continued for several minutes after cessation and respiration. The heart's blood, drawn immediately after death, was of a dark red color; clotting occurred within a few seconds but with little retraction of the clot and separation of serum.

The results of the analyses of various body tissues of these experimental animals are recorded in Table 4.

TABLE 4.—FLUORINE CONTENT (%) OF TISSUES IN EXPERIMENTAL CASES OF POISONING BY FLUORIDE AND FLUOSILICATE.

Tissue.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.
Pancreas . . .	0.00036	0.00058	0.00049		
Spleen . . .	0.00039	0.00060	0.00052	0.00148	
Blood . . .	0.00045	...	0.00103		
Kidney . . .	0.00031	0.00064	0.00066	0.00150	0.00123
Brain . . .	0.00014	0.00018	0.00018	0.00048	0.00036
Heart . . .	0.00021	0.00054	0.00051	0.00111	0.00098
Lung . . .	0.00035	0.00063	0.00076	0.00149	0.00122
Liver . . .	0.00036	0.00066	0.00076	0.00150	0.00122
Muscle . . .	0.00020	0.00042	0.00040	0.00102	0.00081
Urine	0.0062		
Femur . . .	0.0393	0.0160	0.0401	0.0281	0.0326
Teeth . . .	0.0300	0.0163	0.0234	0.0234	0.0261
Time of life (hrs.)	26	7	9	8	8
Weight (kg.) .	9.1	11.2	9.2	9.5	9.8

The data of Tables 3 and 4 bring out the following points of interest: (a) In acute deaths, the fluorine content of the internal organs in humans is within the same range as in dogs, namely, 0.00014 to 0.0016% (0.14 to 1.6 mg. in 100 gm.). (b) The amount of fluorine found in the tissues in fatal cases of poisoning by sodium fluosilicate was approximately the same as that found when death was caused by sodium fluoride. (c) The fluorine content of the brain in every case was somewhat smaller than that of any other organ. (d) The fluorine content of the muscles was somewhat lower than the organs but a little higher than the brain. (e) The fluorine content of the bones and teeth no doubt has also increased but the increase cannot be calculated because of the wide variation of their normal fluorine content. (f) The fluorine content of the urine may vary a great deal: in 1 case it was approximately 10 times that of the tissues.

In order to determine whether there is an accumulation of fluorine in the various organs during chronic fluorine poisoning, the following experiment was conducted. Each of the 2 dogs (6 and 7) was given 18 mg. and 32 mg. of sodium fluoride per kilo of body weight respectively, every day for a period of 2 weeks. The animals were destroyed 48 hours after the ingestion of the last dose, and the tissues were subjected to analysis. Some of the tissues of 2 normal dogs (8 and 9) were used in control analyses. The results of these analyses are recorded in Table 5.

TABLE 5.—FLUORINE CONTENT (%) OF TISSUES IN NORMAL AND CHRONIC FLUORINE CASES.

Tissue.	Chronic.		Normal.	
	Dog 6.	Dog 7.	Dog 8.	Dog 9.
Pancreas	0.000020	0.000042	...	0.000027
Spleen	0.000021	0.000041
Blood	0.000023	0.000033	0.000025	0.000028
Kidney	0.000040	0.000042
Brain	0.000031	0.000035	0.000031	
Heart	0.000050	0.000041	0.000044	
Lung	0.000022	...	0.000040	
Liver	0.000031	0.000043	0.000026	0.000048
Muscle	0.000033	...	0.000030	
Femur	0.0200	0.0182	0.0250	0.0269
Teeth	0.0313	0.0142	...	0.0203

The results of this experiment indicate that the continued ingestion of small amounts (18 and 32 mg.) of NaF per kilo per day for a period of 2 weeks does not result in any accumulation of fluorine in the internal organs. The reason why the organism can tolerate doses as large as these (which in the average man would amount to about 1 gm. of fluorine per day) is twofold: (a) The absorption of fluorine from the intestines is relatively slow, due to the conversion of some of the soluble fluoride into difficultly soluble calcium fluoride; and (b) fluorine in the circulation is very rapidly excreted by way of kidneys.

7. **The Minimum Lethal Dose of Fluorine.** Various values for the lethal dose of fluorine have been reported. In a case reported by McNally,⁴³ the dose taken was 4.5 to 5 gm. of 90% NaF. Luh-rig^{41a} reports a fatal case of poisoning from 4 gm. ($\frac{1}{2}$ teaspoonful) Na_2SiF_6 . Wieland and Kurtzahn⁷³ estimate the fatal dose of Na_2SiF_6 as 0.045 to 0.09 gm. per kilo. Baldwin⁵ cites 3 cases that recovered from 5, 6 and 9 gm. of NaF each, taken in wheat cakes. He himself took 0.03 gm. NaF with no ill-effects, but 0.25 gm. gave him nausea which lasted about 24 hours. Marcovitch⁴⁴ estimates the lowest lethal dose of NaF to be 30 gm. (approximately 0.4 gm. per kilo) and that of Na_2SiF_6 as 7.2 gm. (0.1 gm. per kilo). Starkenstein, Rost and Pohl⁶⁵ state that the fatal dose of NaF is 0.1 to 0.2 gm. per kilo while that of Na_2SiF_6 is 0.04 to 4.14 gm. per kilo. Fullerton³² reports a case in which death occurred after the ingestion of approximately 4 gm. of NaF, and Gellerstedt²⁴ estimates that as little as 0.7 gm. of Na_2SiF_6 has caused death.

The reason why such wide variations as to the lethal dose exists may be (a) the amount of fluorine actually taken by the subject is only a guess; (b) some of the ingested fluorine is lost in the vomitus; (c) the fluorine remaining in the gastro-intestinal tract (unabsorbed) has no bearing on the cause of death; that part of the poison which has been absorbed into the circulation and tissues is solely responsible for the death of the individual; (d) fluorine is very rapidly excreted in the urine.

More accurate information on the minimum lethal dose exists when the experimental data obtained by animal experimentation are considered, although here also there is some disagreement. Heidenhain²⁹ found that 0.05 to 0.1 gm. of NaF per kilo intravenously to a dog was fatal. Sollmann⁶¹ states that 8-mg. daily doses of NaF per kilo of body weight to rats produced no deleterious effect within 9 weeks, but 15 to 150 mg. per kilo resulted in progressive impairment of both growth and food consumption, with little mortality and no histologic lesions. Marcovitch⁴⁴ reports that 6.06 mg. of fluorine (as Na_2SiF_6) per kilo introduced into a rabbit intravenously was fatal in 2 minutes. Leake³⁹ states that the minimum lethal dose for rabbits intravenously is 0.0875 gm. NaF per kilo. Muehlberger⁴⁷ found 20.8 mg. of fluorine (as NaF) to be a lethal dose for rats when administered subcutaneously. Goldemberg²⁵ found the minimum lethal dose by the intraperitoneal route to be 12.7 to 15.8 mg. of fluorine (as NaF) per kilo of body weight.

Muehlberger⁴⁷ determined the relative toxicities of NaF, Na_2SiF_6 , and BaSiF_6 on rats and rabbits. His data seem to confirm the statement of Wieland and Kurtzahn⁷³ that fluorides and fluosilicates are toxic in proportion to their fluorine content. Weight for weight the latter is 3 to 4 times more toxic than the former.

This is what might have been expected, for Na_2SiF_6 is partly converted to NaF and SiF_4 in pure water solution, while in alkaline solution the reaction $\text{Na}_2\text{SiF}_6 + 4\text{NaOH} = 6\text{NaF} + \text{Si(OH)}_4$ takes

place rapidly. Since the intestine is an alkaline medium, it is only natural to suppose that when fluosilicates are ingested this change occurs almost completely before absorption occurs.

In order to test the validity of this supposition, attempts were made to establish the presence of fluosilicate ions in the intestinal tract of the dogs to which this substance had been administered. To a few drops of intestinal washings on a celluloid microscope slide was added a drop of sodium chloride solution. No crystals of Na_2SiF_6 were observed under the microscope. Similar attempts to obtain the crystals of BaSiF_6 were also unsuccessful. In order to rule out the possibility that all of the fluosilicate had already been absorbed, the presence of fluorine in the intestinal washings was demonstrated by the application of the hanging drop test with the production of crystals of Na_2SiF_6 .

It was our intention to calculate the minimum lethal absorbed dose of fluorine (exclusive of the gastro-intestinal tract) from the analysis of the various organs and tissues. This was impossible, however, because of the fact that fluorine accumulates in the bones, teeth, fat, skin, hair and nails, during life, from the daily diet, and since the normal fluorine content of these tissues varies over a wide range and is not known for any specific case, the amount of absorbed fluorine in these tissues originating from the dose of fluorine cannot be estimated. We have therefore simply calculated the minimum absorbed lethal dose in the body exclusive of bones, teeth, fat, skin, hair and nails.

TABLE 6.—LETHAL FLUORINE CONTENT OF INTERNAL ORGANS.

	Weight (gm.) of organ in body of 140 lbs.	Fluorine % of wet tissue smallest found.	Smallest amount of fluorine (mg.) in entire organ.
Brain	1,250	human 0.00016 dog 0.00014	1.75
Liver	1,500	human 0.00040 dog 0.00036	5.40
Kidneys	300	human 0.00046 dog 0.00031	1.14
Heart	300	dog 0.00021	0.63
Lungs	800	dog 0.00035	2.80
Spleen	150	dog 0.00039	0.58
Pancreas	100	dog 0.00036	0.36
Muscles	30,000	dog 0.00026	78.00
Blood	4,000	human 0.00035 dog 0.00035	14.00
Total wt. analyzed organs.	38,400	104.66
Bones, fat, G.I. tract, skin, hair, etc.	24,600	Not included	Not included
Total body wt.	63,000		

The data of Table 6 bring out the following points: (a) The smallest lethal dose of fluorine absorbed into the internal organs in our cases was 104.66 mg. (calculated to a body weighing 63 kilos= about 140 pounds). For bodies of different weight, the fluorine content of the organs can be calculated by using the values in the per cent column; (b) multiplying the combined fluorine content of

the liver and the brain by 15, one obtains a fair estimate of the total amount of fluorine present in all of the internal organs.

8. Symptoms of Fluorine Poisoning. *Acute poisoning:* from NaF or Na_2SiF_6 *per os*: (1) Gastro-intestinal disturbances: nausea, vomiting, purging, convulsive pains in abdomen. (2) Salivation and lachrymation. (3) Pulmonary disturbances: acceleration and deepening of respiration followed by dyspnea. (4) Cardiac insufficiency and cardiac weakness. (5) Motor and sensory disturbances: tremors and convulsions which may involve only a part or the whole body, and may assume an epileptic character. These symptoms, according to Tappeiner⁶⁸ are not of a reflex nature, and are not dependent upon disturbances of the respiration and circulation, but originate in the spinal cord and higher centers. Paralysis of the vasomotor center; patient may be unable to open his mouth; loss of speech. *Disorder of sensibility of fingers.* *Convulsive pains in legs, and uncertainty of gait.* (6) Signs of renal irritation, albumin in urine and edema. (7) Terminal stage: general exhaustion, loss of consciousness, respiratory paralysis. Heart continues to beat a minute or two after cessation of respiration. Death in several hours.

Acute poisoning with a solution of hydrofluoric acid *per os*: There is severe pain in abdomen almost immediately, with vomiting and purging. Many of the symptoms listed under sodium fluoride poisoning are also in evidence. Death results from cardiac paralysis and occurs in 1 to 6 hours.

Acute poisoning by inhaling hydrogen fluoride gas: The inhalation of HF is very deleterious. The Belgian chemist, Louyet, died from the inhalation of the gas, while experimenting with it. Severe laryngitis and bronchitis result. The lesions are ulcerations of the conjunctiva, nose, mouth and gums. Severe pain in throat and stomach, with vomiting and collapse.

Action of a hydrofluoric acid solution upon the skin: The solution of this acid in contact with the skin produces severe and very painful burns and blisters, which heal very slowly.

Chronic Poisoning. From small daily doses of sodium fluoride: Sollmann⁶¹ states that 8-mg. daily doses of NaF per kilo of body weight in rats, for 9 weeks, produced no deleterious effects on growth or food consumption. Daily doses of 15 to 150 mg. of NaF per kilo body weight resulted in progressive impairment of growth and food consumption, little mortality, with no histologic changes. In our experiments, 18 and 32 mg. daily doses per kilo for 2 weeks produced no symptoms except that the dogs lost their appetite. After somewhat larger amounts, 50 to 100 mg. per kilo for several months, the animal walked with difficulty, his back sagged, hair fell out and teeth chipped off.

9. Postmortem Findings. Due to swallowing of alkali fluorides: Premature rigor mortis. Severe hemorrhagic gastritis, swelling and corrosion of stomach mucosa with dark red discoloration, and extravasations of blood. The dark crimson discoloration of the rugæ is

very pronounced. Veins are filled with viscous dark red blood. Kidneys give evidence of nephrosis.

Due to swallowing a solution of hydrofluoric acid: The buccal mucous membrane is white; the tongue, gums, epiglottis and esophagus are denuded of epithelium; the mucous membrane of the stomach is softened and corroded, very dark, almost black discoloration of the rugæ and intensely red and ecchymosed in the depressions.

10. Treatment. For alkali fluorides and fluosilicates taken internally: (1) Abundant stomach wash with lime water, milk, or an aqueous suspension of finely divided medicinal charcoal; (2) administer castor oil as a purgative; (3) give plenty of fluids in order to flush the system. For burns of the skin due to hydrofluoric acid: Quick action is essential. Thoroughly wash the affected skin with a 5% solution of soda-lime. Avoid rubbing the skin. Then bathe the affected portions in 1% soda-lime solution for about $\frac{1}{2}$ hour, and apply some butesin picrate salve.

Summary. 1. Various qualitative tests and quantitative determinations for fluorine are discussed from the standpoint of their applicability to tissue analysis.

2. The technique, which in our hands gave the best result, for the detection and quantitative determination of fluorine, is described.

3. The normal fluorine content of the various human organs and tissues has been determined.

4. The distribution of the fluorine into the various organs and body tissues of fatal fluoride cases has been determined.

5. The minimum lethal absorbed dose of fluoride has been estimated.

6. The symptoms of fluorine poisoning are described.

7. Postmortem findings in fatal fluoride cases are described.

8. The treatment for fluoride poisoning is outlined.

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A PHARMACOLOGIC STUDY OF TRICHLORETHANOL.

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TRICHLORETHANOL is the alcohol corresponding to the aldehyde, chloral. It resembles tribromethanol in structure, but contains chlorine in place of bromine. Trichlorethanol has received little

attention, although it is thought to be formed in the body from chloral hydrate. Its narcotic potency was briefly described by Külz,³ and Akamatsu and Wasmuth;¹ it has been studied more recently by Molitor.⁵ From our earlier studies,^{2,4} trichlorethanol appeared to have possibilities for use as a basal anesthetic. We have investigated its anesthetic effect alone and in combination with ether, its action on respiration and circulation, its fate in the body, its action on carbohydrate metabolism and acid-base balance, and on the histology of mucous membranes, heart, liver and kidney.

Trichlorethanol* has been compared with two forms of tribromethanol, crystals† and a solution in amylene hydrate ("Avertin-Fluid," "Avertin with Amylene Hydrate, N.N.R.").‡ Throughout the paper, doses are given in grams per kilogram of body weight. In the case of tribromethanol, this refers to this substance alone, whether used as crystals or the solution in amylene hydrate.

Trichlorethanol is readily handled in the pure state, being liquid above 18° C. Its specific gravity is such that 1 cc. contains 1.55 gm. This is an important difference from "Avertin-Fluid," 1 cc. of which contains 1 gm. of tribromethanol. Trichlorethanol is more soluble in water than is tribromethanol. Table 1 shows its solubility, as determined indirectly with the Abbé refractometer. The greater solubility at lower temperatures prevents trichlorethanol from separating out of solution on cooling, as is the case with tribromethanol. Aqueous solutions of trichlorethanol are more stable than those of "Avertin-Fluid" (Fig. 1), but precautions similar to those taken with the latter should be followed.

TABLE 1.

Temp., ° C.	Grams per 100 cc. water.
0	10.04
20	8.82
25	8.35
37	7.86

1. *Anesthetic Activity.* In depressing the central nervous system, trichlorethanol and tribromethanol are qualitatively and quantitatively similar,⁴ compared weight for weight. The effective doses are shown in Table 2. Trichlorethanol appears to have a wider margin of safety, in that it produces sleep and anesthesia in smaller fractions of the fatal dose. This difference has also been noted by Molitor.⁵ Death seems to result from respiratory paralysis.

The duration of narcosis and postanesthetic depression with trichlorethanol is slightly greater than with "Avertin-Fluid," and considerably greater than with crystalline tribromethanol (Figs. 2 and 3). The onset of action with rectal administration is slower with

* Prepared by Dr. R. R. Burtner at G. D. Searle & Co. Subsequently we have used some supplied by Merck & Co.

† Prepared by Dr. Burtner.

‡ Winthrop Chemical Company. Purchased.

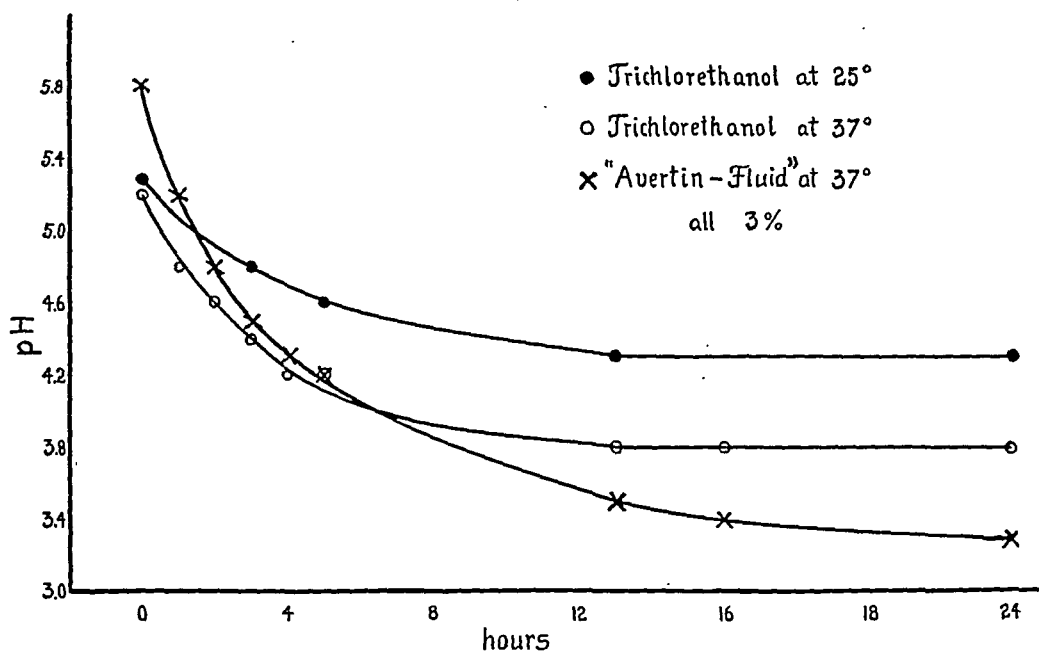


FIG. 1.—Rate of decomposition of 3% aqueous solutions of trichlorethanol and "Avertin-Fluid." Concentration of hydrogen ions determined by the indicator method.

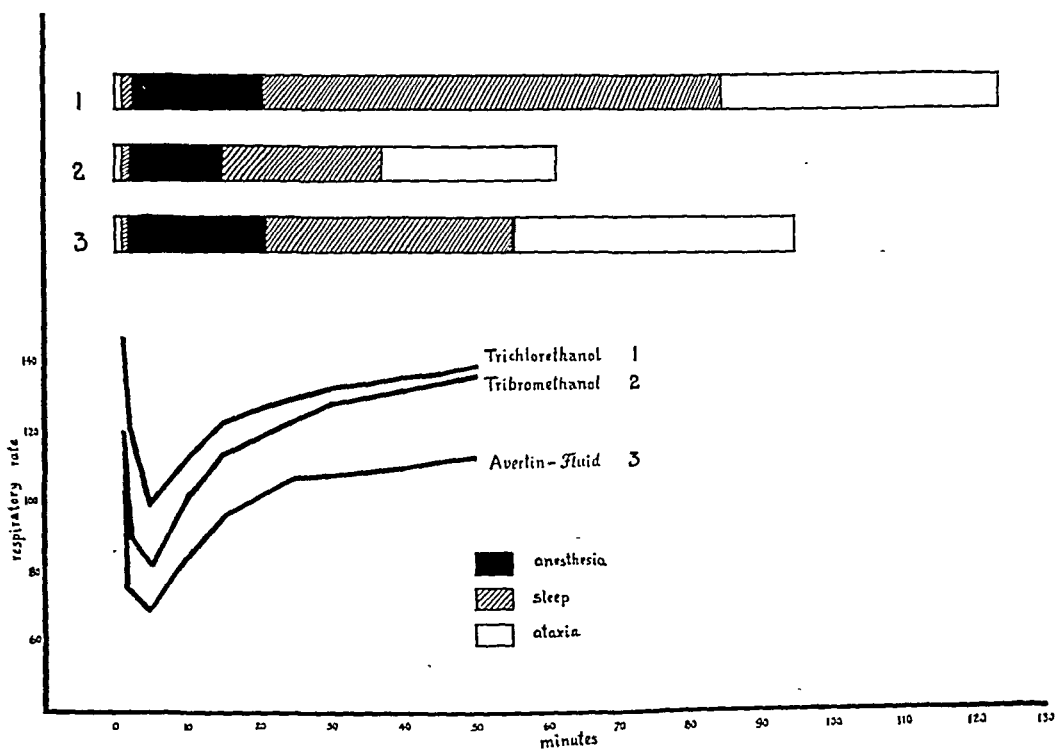


FIG. 2.—Average duration of anesthesia, sleep and ataxia, and respiratory rates in 30 rats, receiving at 1-week intervals intraperitoneal injections of 0.3 gm. per kilo of trichlorethanol, tribromethanol and "Avertin-Fluid" in 3% solutions.

trichlorethanol than with the tribromethanol preparations. The greater duration of action with trichlorethanol is probably to be explained by the fact that in equal weights of trichlorethanol and

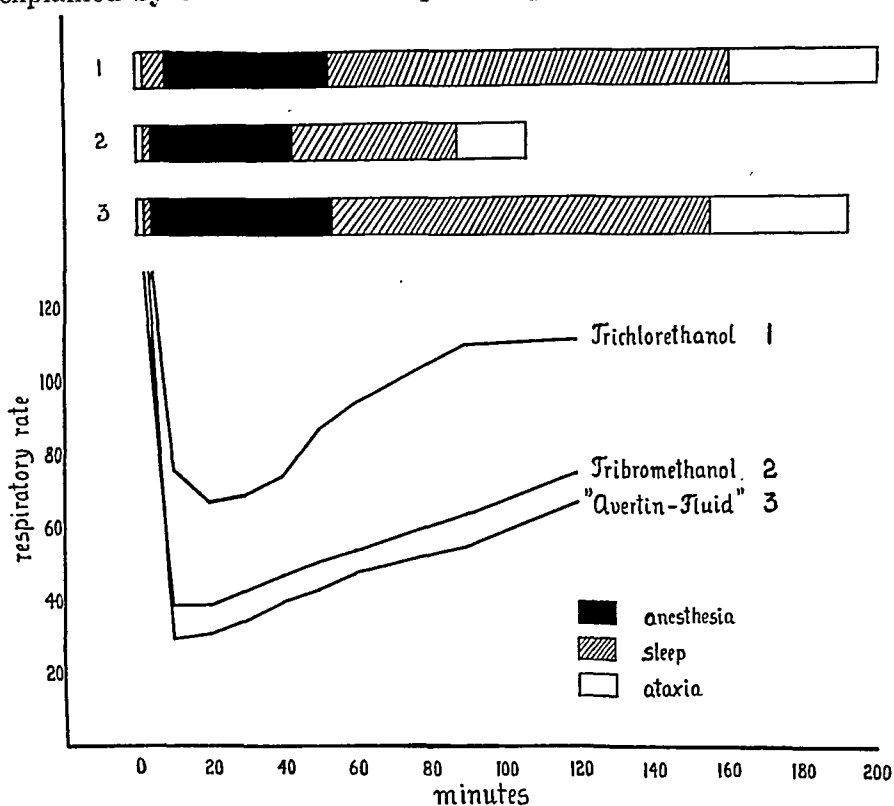


FIG. 3.—Average duration of anesthesia, sleep and ataxia, and respiratory rates after rectal administration of 0.4 gm. per kilo of 3% solutions of trichlorethanol in 14 rabbits, tribromethanol in 7 rabbits and "Avertin-Fluid" in 10 rabbits.

tribromethanol, there are twice as many molecules in the former as in the latter. With "Avertin-Fluid" the amylene hydrate contributes to the narcotic action, so that its duration is about the same as with trichlorethanol.

TABLE 2.

	Trichlorethanol, 3%, gm. per kilo.			Tribromethanol, 3%, gm. per kilo.		
	By mouth in rats.	Intraperitoneally in rats.	Intravenously in rabbits.*	By mouth in rats.	Intraperitoneally in rats.	Intravenously in rabbits.*
Minimum hypnotic dose .	0.20	0.10	0.04	0.27	0.10	0.045
Minimum anesthetic dose .	0.60	0.15	0.12	0.60	0.20	0.100
Minimum fatal dose . .	1.00	0.40	0.18	1.00	0.45	0.180

* Duration of injection: 90 seconds.

The analgesic, apart from the narcotic, action is no greater with trichlorethanol than with tribromethanol.

2. *Local Action on Mucous Membranes.* The 3% solutions of all three compounds are without discernible influence on the gastric mucosa and the rectal mucosa. They have a local anesthetic action on the rabbit's cornea, but they cause a marked conjunctivitis.

3. *Action on Respiration.* Trichlorethanol depresses respiratory rate and volume but much less than does tribromethanol (Figs. 2 and 3, and in additional detail⁴). Here again, the presence of amylene hydrate in "Avertin-Fluid" contributes significantly. Since the chief danger in clinical use of "Avertin-Fluid" is serious respiratory depression, trichlorethanol is perhaps preferable.

4. *Action on Circulation.* Trichlorethanol and tribromethanol are equally active in producing a fall in arterial pressure,⁴ as a result of depressing the medullary and spinal vasomotor centers. Cardiac function seems to be unimpaired when therapeutic doses are administered. Electrocardiographic records in the experiments of Section 7 showed no disturbance of rhythm or conduction. No histologic change was observed in the hearts of the animals mentioned in Section 8.

5. *Action on Alkali Reserve and Blood Sugar.* Plasma carbon dioxide combining capacity⁷ and blood sugar, according to Hagedorn and Jensen, were determined after rectal administration of 0.4 gm. per kilo in rabbits (Table 3). The values of "blood glucose" after administration of the drugs are not to be interpreted as glucose alone. They include glucose and the glucuronic acid which has been conjugated with the drugs in the process of detoxification. The actual blood glucose values cannot be ascertained from these figures. The higher values found after administration of trichlorethanol are explained here also by the difference of molecular equivalents, when the same amount in grams is given.

The alkali reserve is lowered to about the same extent with trichlorethanol and "Avertin-Fluid," as indicated by the average values. In both cases the fall is of minor importance.

6. *Fate in the Body. Tolerance.* As mentioned above, trichlorethanol is detoxified in the body through conjugation with glucuronic acid to give urochloralic acid which is excreted in the urine. The amount of urochloralic acid excreted in the urine of dogs varies, but apparently never reaches the theoretical maximum, if the trichlorethanol were all excreted in this form. It depends probably on the diet of the dogs before the experiment is started, since Quick⁶ has shown that a carbohydrate diet increases the amount of glucuronic acid in a normal animal. In 1 case we could isolate 20% of the administered trichlorethanol unchanged.

Also of interest is the rate of excretion. The urine of men receiving 2-gm. doses of trichlorethanol was collected at 90-minute intervals, and 10 cc. of it were acidified and extracted with ether for 4 hours.

After evaporation of the ether and hydrolysis with dilute HCl, the amount of reducing substance was determined by the Hagedorn-Jensen sugar method. Figure 4 shows the results of such an experiment, expressed as glucose equivalents. The excretion remains at a high level for 6 hours and then falls rapidly.

TABLE 3.

Plasma CO ₂ combining capacity, vol. %.						Blood sugar, mg. %.									
3% trichlorethanol, 0.4 gm./kilo rect.			3% "Avertin- Fluid," 0.4 gm./kilo rect.			3% trichlorethanol, 0.4 gm./kilo rect.				3% "Avertin-Fluid," 0.4 gm./kilo rect.					
Rabbit No.	Normal.	2 hrs. after injection.	Rabbit No.	Normal.	2 hrs. after injection.	Rabbit No.	Normal.	After injection.			Rabbit No.	Normal.	After injection.		
								1 hr.	2 hrs.	3 hrs.			1 hr.	2 hrs.	3 hrs.
1	47.3	36.9	9	41.9	36.6	1	115	194	281	385	9	114	130	182	195
2	55.1	51.4	10	42.6	34.0	2	107	135	175	192	10	121	132	158	159
3	42.9	35.3	11	48.6	33.8	3	110	226	409	460	11	119	173	233	212
4	46.0	29.8	12	50.2	41.6	4	126	172	177	210	12	121	133	182	196
5	47.0	24.4				5	115	189	186	192					
6	60.0	52.5				6	120	172	176	177					
7	47.1	33.0				7	118	156	274	267					
8	50.4	36.4													
Av.	49.5	37.5	Av.	45.8	36.5	Av.	116	178	239	269	Av.	119	142	189	190

The occurrence of tolerance to trichlorethanol and "Avertin-Fluid" was examined by daily oral administration of 0.6 gm. per kilo to rats. The results are not uniform as Table 4 shows. Some rats seem to have acquired tolerance, particularly to "Avertin-Fluid," some of them seem to have lost it.

TABLE 4.

Rat No.	Duration of loss of posture in minutes.						
	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	7th day.
3% Trichlorethanol.							
1	180	186	180	28	210	200	157
2	250	258	267	325	*		
3	167	240	177	165	173	145	142
4	160	132	137	120	142	139	119
5	196	201	229	251	176	Killed	
6	176	233*	240	Killed			
7	224	239	218	227	243	202	236
3% "Avertin-Fluid."							
8	144	69	*				
9	149	123	110	113	0	41	60
10	189	124	136	101	87	Killed	
11	137	97	13	13	10	26	7
12	200	134	182	*			

* Died during anesthesia.

7. *Action as a Basal Anesthetic.* Four dogs were given rectally 0.2 gm. or 0.3 gm. per kilo of trichlorethanol, and 5 days later 3 of these dogs received corresponding doses of "Avertin-Fluid." Respiratory rate was noted and electrocardiograms taken immediately before and 20 minutes after the administration. Then ether was given by inhalation so that the wink reflex was abolished in about 10 minutes. Arterial blood was then taken and its ether content determined by aëration into standardized chromic acid and iodimetric titration. Ether inhalation was continued until respiration ceased, when blood-ether content was again determined (Table 5). It appears that with trichlorethanol less ether is required than with "Avertin-Fluid."

8. *Histologic Studies.* These were made in three series of animals:

(a) Six rabbits receiving by rectum 0.4 gm. per kilo of trichlor-

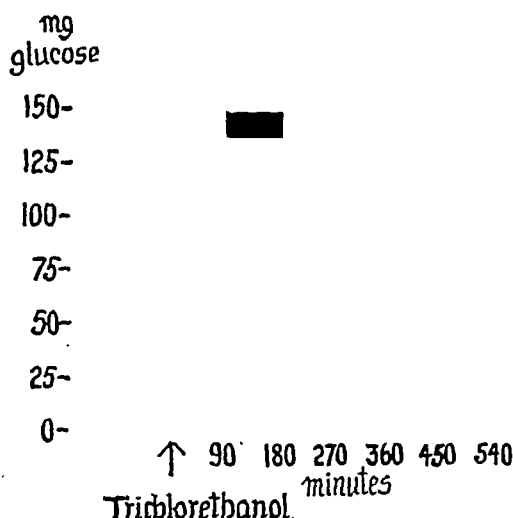


FIG. 4.—Rate of excretion of urochloralic acid in man after oral administration of 2 gm. trichlorethanol.

ethanol in 3% solution, and 2 rabbits receiving the same dose of "Avertin-Fluid" were killed after 24 hours. Heart, liver and kidney were found to be normal.

(b) Seven rats received daily 0.6 gm. per kilo of trichlorethanol by mouth, and 5 rats the same dose of "Avertin-Fluid" (Table 4). The surviving animals were killed on the eighth day, and the hearts, livers and kidneys of all the animals were examined histologically. Of the 7 rats receiving trichlorethanol, the livers of 2 (Nos. 1 and 7) showed moderate histologic changes, the one cloudy swelling and fatty degeneration, the other cloudy swelling and atrophy. Hearts and kidneys of these 2 rats were normal. The organs of the rats which had received "Avertin-Fluid" were normal, with the exception of 1 rat, the liver of which showed slight cloudy swelling. The kidney of this rat was severely damaged, with in-

flammatory infiltration in tubuli and glomeruli, some cloudy swelling and necrosis.

(c) The effect of trichlorethanol and "Avertin-Fluid" on a previously damaged liver was examined by the following experiment: In 14 rats, liver damage was produced by the oral administration of 1.5 cc. per kilo of a 1 to 1 mixture of carbon tetrachloride and ethyl alcohol. Twenty-four hours later 5 of these rats were given orally 0.5 gm. per kilo of trichlorethanol, and 5 the same dose of "Avertin-Fluid." These rats were highly susceptible to the anesthetics. Four of the rats which had received "Avertin-Fluid" died during anesthesia. Even a higher dose, 0.6 gm. per kilo, does not kill normal rats. Trichlorethanol had less effect. Only 1 of the 5 rats died, but the average duration of the action in the 4 surviving animals was 295 minutes, compared with 135 minutes in normal rats.

The livers of the 4 rats which received the carbon tetrachloride-alcohol mixture alone showed extensive damage near the central veins, with fatty degeneration and infiltration, and areas of recent necrosis, some with hemorrhages. Most of the lobules were involved. The kidneys exhibited small hemorrhages in the glomeruli, focal areas of necrosis, severe cloudy swelling and more diffuse areas of fatty degeneration.

TABLE 5.

Dog No.	3% Trichlorethanol						3% "Avertin-Fluid"					
	Heart rate. Injection.		Respiratory rate. Injection.		Blood ether content, mg. %.		Heart rate. Injection.		Respiratory rate. Injection.		Blood ether content, mg. %.	
	Before.	20 mins. after.	Before.	20 mins. after.	Wink reflex abolished.	Respiration ceased.	Before.	20 mins. after.	Before.	20 mins. after.	Wink reflex abolished.	Respiration ceased.
1. 0.3 gm./kilo rectally	115	125	21	22	65	123	78	90	24	27	138	176
2. 0.2 gm./kg. rectally	130	120	20	24	72	134						
3. 0.2 gm./kg. rectally	92	87	30	34	59	109	69	103	120	280	141	189
4. 0.3 gm./kilo rectally	106	112	22	18	115	149	96	160	47	81	152	171

The administration of the two anesthetics did not increase the extent of the pathologic change already caused by the carbon tetrachloride-alcohol mixture.

Conclusions. Trichlorethanol has an anesthetic action resembling that of tribromethanol and "Avertin-Fluid," but trichlorethanol is less depressant to respiration and has a wider margin of safety. In its action on the circulation, on blood-alkali reserve and on mucous membranes it resembles tribromethanol.

Trichlorethanol is excreted in the urine in conjugation with glucuronic acid and partly unchanged. Tolerance to it is not readily developed.

Trichlorethanol does not produce constant histologic changes in heart, liver or kidney, even after repeated administration. It does not augment a previously existing damage to liver or kidney, but under such circumstances its action is greatly prolonged.

With trichlorethanol used as a basal anesthetic, less ether is required to produce loss of reflexes and cessation of respiration than with tribromethanol.

Trichlorethanol is more soluble in water than is tribromethanol. Its aqueous solutions are more stable than those of tribromethanol.

Trichlorethanol seems deserving of clinical trial.

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SIGNIFICANCE OF STANDARD LABORATORY PROCEDURES IN THE DIAGNOSIS OF BRUCELLOSIS.

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SINCE 1918, when Evans^{4a} demonstrated the close relationship of Bang's *B. abortus* and Bruce's *M. melitensis*, there has been in the United States a steadily increasing interest in the disease now known as brucellosis. The great diversity of signs and symptoms produced by this infection compels the clinician to rely upon the laboratory for diagnosis.

Complement fixation as a routine procedure for the diagnosis of brucellosis has been generally discarded, since it offers no advantages over the more simply performed agglutination test. The agglutination test *per se* has not proven to be entirely satisfactory, since various investigators^{2,4b,13} have reported proven cases of acute and chronic brucellosis without agglutinins, and Dooley,³ in a study of 263 students, found agglutinins in 108, only 2 of whom had clinical symptoms of the disease.

Skin tests with different type antigens have been studied by several investigators^{1,5,7,12,15} who have generally concluded that the endermic reactions are of aid in diagnosis but have limited value, since patients can often develop an allergic cutaneous reaction without showing symptoms of disease. Moreover, skin sensitivity persists after complete recovery.

It is evident that none of the preceding tests alone, or combinations of them, are to be relied upon in determining the exact immunologic status of a patient. Huddleson,¹¹ in 1933, devised an ingenious and fairly simple method of determining the opsonocytophagic power of human blood. Using this test, in conjunction with the allergic skin test and agglutinins, he was able to classify all patients into three groups: susceptible, infected and immune.

The object of this paper is to report the result of a survey made by us in an effort to correlate the results of these immunologic procedures with the clinical impressions as determined by history, observations and physical examination. Previous surveys have been done either on groups whose occupational hazard for infection was great, groups who were known to be drinking contaminated milk, or hospitalized patients who were suffering from various known or unknown diseases. We decided to study only healthy individuals who had no known exposure to the disease. We found 1122 male Duke University students who were willing to coöperate, none of whom had any past history of acute or chronic illness suggestive of *Brucella* infection. Physical examination revealed no abnormalities, and none had complaints at the time of the study. These students came from all 48 states and 7 foreign countries, the majority, however, from the Middle Atlantic and southern sections of this country. In addition to the students used for this survey, we studied carefully a few selected hospital patients, who will be reported at this time since they illustrate some pertinent points.

Technique of Tests. *Cutaneous.* One-tenth cubic centimeter of a 1 to 2000 dilution of brucellergin,¹⁰ a nucleoprotein derived from *Brucella* organisms, was injected into the skin of the flexor surface of the forearm. The tests were read 48 hours after injection, noting the erythema, edema, and induration. If read before 48 hours, the commonly occurring early false reactions may give an erroneous impression. These false reactions are characterized by inflammation without induration or edema and usually subside rapidly after 18 to 24 hours.

Agglutination. The usual macroscopic method was employed, using serial dilutions of serum from 1 to 20 to 1 to 5120 and a control. The antigen was an equal mixture of *Brucella*, varieties *abortus* 456 and *melitensis* 428. The organisms were grown on liver infusion agar at 37° C. for 2 days. The growths of each strain were washed off in normal physiologic saline, which contained 0.5% formalin and diluted to equal densities. Equal amounts were mixed and the resulting suspension diluted with normal saline to a density of 7 cm. on the Gates apparatus.

Huddleson's¹⁰ rapid agglutination slide test also was used as a check on all sera, but no appreciable differences could be detected.

Opsonocytophagic Test. Huddleson's¹⁰ technique, with minor variations, was followed. Whole blood (5 cc.) was collected in a Wassermann tube containing 0.2 cc. of a 20% solution of sodium citrate in normal saline. The tube was stoppered and gently inverted several times. One-tenth cubic centimeter of the resulting 0.8% citrated blood was removed and placed in a second Wassermann tube. To this was added 0.1 cc. of a heavy (1.0 cm. Gates) normal saline suspension of a 48-hour culture of *Brucella*, variety *abortus* 456. The tube was placed in a 37° C. water bath and was gently shaken at 10-minute intervals. After 30 minutes the tube was removed, the cells were resuspended, and a drop, obtained with a capillary pipette, was placed on a clean polished slide. Smears were drawn in the usual manner. After rapid drying in hot air they were stained by Wilson's method. Fifty segmented neutrophils were counted and a phagocytic index number derived according to the method of Foshay and LeBlanc.⁶

Sedimentation Rate. The sedimentation rate of the R. B. C. was determined by the Wintrobe method.¹⁴

Results. One hundred and twenty-seven students, or 11.3% of the 1122 students who were skin-tested, gave a positive reaction. It was decided to use these 127 positive reactors for further study and to control the work with 127 students who had negative skin tests.

Of the 127 positive reactors, 114 (89.8%) stated that they drank raw milk in their homes. In comparison, only 46 (36.2%) of the 127 who failed to react gave a history of using raw milk. None in either group had ever had any known contact with infected animals or meat, nor had any ever worked in a laboratory.

The local reactions varied in size from 1.5 by 2 cm. to 8 by 14 cm. Forty-three, or approximately one-third of the group who reacted, had an accompanying lymphangitis; 22 of these complained of tender axillæ, and painful axillary lymph nodes were easily palpable. Twenty-four students had systemic reactions characterized by fever, chills, headaches, myalgia, arthralgia and general malaise. These symptoms usually subsided in 12 to 18 hours and required nothing more than small doses of acetylsalicylic acid. However, 5 students had a fever of 40° C. (104° F.) or higher, and required hospitalization for 3 or 4 days. One student reacted so severely that the skin sloughed over an area of 6 by 4 cm., but the lesion healed spontaneously after a 9-week period. There was no correlation between the amount of local and systemic reactions and the antibody content as evidenced by the opsonocytophagic and agglutination tests. Several students with very marked skin reactions showed little or no evidence of antibodies, while others with only very small local reactions had high antibody titers. All the severe systemic reactions were accompanied by marked local reactions.

The immunologic studies done at the time of reading the skin tests are tabulated in Table 1.

Applying Huddleson's¹⁰ system of classification, 995 (88.7%) of the 1122 clinically well students were susceptible, 116 (10.4%) infected, 6 (0.5%) questionably immune and 3 (0.25%) immune.

Sedimentation rates on the different groups are shown in Table 2.

Goldstein,⁸ Heathman⁹ and Huddleson¹⁰ demonstrated the appearance of agglutinins after skin testing, and Evans^{4c} showed that agglutinins and opsonocytophagic index power are often increased following endermic injections. The results obtained on 20 students with positive skin reactions are in Table 3. The agglutinins and opsonocytophagic reactions slowly decreased after the third week.

TABLE 1.—RESULTS OF IMMUNOLOGIC STUDIES IN 127 SKIN-TEST POSITIVES AND 127 NEGATIVES.

		Agglutinins.						Opsonocytophagic index.					
No.	Positive skin test.	0.	1-20.	1-40.	1-80.	1-160.		0.	1-20.	21-30.	31-60.	61-80.	81-100.
127	127	97	13	10	4	3		2	51	45	18	6	3
127	0	125	2	0	0	0		89	34	3	0	1	0

TABLE 2.—SEDIMENTATION RATE STUDIES.

Group.	Average sedimentation rate, mm. per hr.
127 susceptible students	5.3
116 infected students	4.9
6 questionably immune	5.1
3 immune	5.0

TABLE 3.—EFFECT OF BRUCELLERGIN SKIN TESTS ON AGGLUTININS AND OPSONOCYTOPHAGIC POWER.

Case.	At time of injection.		7 days later.		14 days later.		21 days later.	
	Aggl.	Opsono. index.	Aggl.	Opsono. index.	Aggl.	Opsono. index.	Aggl.	Opsono. index.
1	1-40	74	1-160	90	1-640	92	1-640	98
2	0	26	1-40	24	1-80	40	1-80	44
3	0	18	0	22	1-80	30	1-80	24
4	0	16	1-160	14	1-320	20	1-320	25
5	0	21	0	30	0	42	0	45
6	1-40	26	1-80	34	1-80	46	1-160	44
7	0	20	0	20	0	16	0	24
8	0	18	0	26	1-40	34	1-80	40
9	0	22	0	20	0	30	1-80	32
10	0	21	0	28	0	35	0	39
11	0	24	0	20	0	31	1-80	38
12	1-160	43	1-320	55	1-640	62	1-1280	78
13	0	22	0	44	0	55	1-80	60
14	0	18	0	24	1-80	30	1-160	32
15	1-20	16	1-80	36	1-80	42	1-320	54
15	0	39	0	60	0	68	1-80	85
17	0	28	0	20	0	38	0	61
18	0	14	0	24	1-40	34	1-160	32
19	1-20	21	1-160	36	1-320	40	1-320	44
20	0	19	0	36	0	42	0	50
Average	..	25.3	..	33.1	..	41.3	..	47.4

Another group of reacting students were followed in the same manner except that typhoid vaccine in the usual immunizing doses was given on the 7th, 14th and 21st days (Table 4).

It is evident from these experiments that the endermic injection of brucellergin causes a rise in the patient's opsonins and agglutinins which reaches a peak near the end of the third week. It is also apparent that when additional foreign protein, in the form of killed typhoid and paratyphoid bacilli, are injected in conjunction with brucellergin, the stimulation is greater and more prolonged, the greatest response being reached around the end of the 7th week.

TABLE 4.—EFFECT OF TYPHOID VACCINE INJECTIONS ON IMMUNOLOGIC FINDINGS.

Case.	At time of injection.		7 days later.		14 days later.		21 days later.		28 days later.		35 days later.		42 days later.	
	Agglutinins.	Opso. index.	Agglutinins.	Opso. index.	Agglutinins.	Opso. index.	Agglutinins.	Opso. index.	Agglutinins.	Opso. index.	Agglutinins.	Opso. index.	Agglutinins.	Opso. index.
1	1-20	28	1-40	36	1-80	48	1-320	55	1-1280	61	1-640	67	1-640	68
2	0	20	0	40	1-320	40	1-640	62	1-640	68	1-640	72	1-1280	74
3	0	18	0	34	0	46	0	45	1-40	50	0	55	1-80	63
4	0	21	0	30	1-40	34	0	40	0	40	0	42	0	44
5	1-20	32	1-80	45	1-320	42	1-640	55	1-640	63	1-640	71	1-320	85
6	0	16	0	20	0	33	0	39	0	48	1-320	61	1-640	73
7	0	25	1-80	33	1-640	50	1-640	64	1-1280	74	1-1280	78	1-1280	70
8	0	8	0	18	0	38	0	40	1-160	44	1-320	38	1-160	36
9	1-40	44	1-80	60	1-80	74	1-80	78	1-160	86	1-640	92	1-640	98
10	0	19	0	35	0	38	0	43	0	50	0	54	0	57
11	0	23	0	38	1-40	51	1-80	59	1-80	62	1-160	67	1-320	76
12	0	22	0	18	0	23	0	36	0	64	0	70	0	84
13	0	31	1-80	44	1-160	48	1-320	53	1-640	61	1-1280	68	1-2560	71
14	0	13	0	19	0	33	0	41	1-40	55	1-80	63	1-160	65
15	0	17	0	31	0	30	0	44	0	48	1-320	52	1-320	50
16	0	23	0	22	0	37	0	39	0	55	0	49	0	48
17	1-160	48	1-320	64	1-640	73	1-640	78	1-1280	90	1-1280	92	1-2560	92
18	1-80	74	1-640	88	1-320	66	1-640	88	1-1280	76	1-5120	84	1-5120	96
Av.	..	28.6	..	37.5	..	44.6	..	53.5	..	60.8	..	65.2	..	69.4

Dooley,³ in 1932, pointed out that fever due to any cause might increase serum agglutinins against *Brucella* whether there had or had not been a previous clinical infection with *Brucella*. This was confirmed by our studies of the 9 students who became ill at various times with proven streptococcic sore throat. Their immunologic reactions toward *Brucella* are expressed in Table 5.

TABLE 5.—EFFECT OF INTERCURRENT STREPTOCOCCAL SORE THROAT ON IMMUNOLOGIC FINDINGS.

Case.	Three weeks prior to illness.		During illness.	
	Agglutinins.	Opsonocytophagic index.	Agglutinins.	Opsonocytophagic index.
1	0	18	1-160	39
2	0	14	1-80	50
3	0	27	1-320	53
4	0	0	1-160	43
5	1-20	28	1-640	76
6	0	5	1-320	47
7	0	17	1-80	39
8	1-20	31	1-1280	88
9	0	23	1-80	64

It appears from this that an unrelated febrile illness may cause not only a rapid increase in serum agglutinins, but also a corresponding increase of opsonocytophagic power against *Brucella* in patients with no previous clinical infection with *Brucella*.

It is a well-known immunologic fact that one may be immune to a disease and yet show no circulating antibodies to the specific antigen. Typhoid fever is a classic illustration of this, and patients who have recovered may not have circulating immune bodies. However, if injections of bacilli or their components are given to such a patient, there is usually a rapid rise of measurable antibodies. It is possible that this principle applies to *Brucella* infections. If, during a survey, the immunologic factors are measured at their peak, a much more accurate picture should be obtained. All students, therefore, who had received merely the endermic brucellergin injection were recalled at the 3d week. The ones who had also been inoculated against typhoid fever were called back at the end of the 7th week. The results of the studies on both groups done at these times are shown in Table 6.

TABLE 6.—INCREASE IN NUMBER OF IMMUNE RESPONSES PRODUCED BY INJECTIONS OF BRUCELLERGIN AND TYPHOID VACCINE.

No.	Agglutinins.						Opsonocytophagic index.					
	0.	1-20.	1-40.	1-80.	1-160.	1-320.	0.	1-20.	21-30.	31-60.	61-80.	81-100
127	29	5	7	16	19	51	0	6	15	49	38	19

When these figures are analyzed it is evident that there has been a rather marked change. The 116 who originally had been classified as infected were now reduced to 70. Those questionably immune had risen from 6 to 38, and the number of immunes from 3 to 19.

These latter studies agree much more closely with the clinical impression than those made earlier. However, it is hard to correlate the fact that 70 students who, from a clinical standpoint, are perfectly well, would be classified as infected by the accepted standards of classification. It must be concluded that most strains of *Brucella* in this country are relatively avirulent or that the infecting dose is very small. In any case, it appears that too much weight should not be given to laboratory findings alone, and that their interpretations must be very guarded. One is probably justified in saying that the patient is infected, but one cannot say that the patient has brucellosis.

The following short summaries of 4 hospital patients illustrate the misleading nature of established laboratory findings.

Case Histories. No. 95169. A 23-year-old graduate student entered Duke Hospital complaining of afternoon fever and chilly sensations of 4 days' duration. Physical examination except for a temperature of 39° C.

(102.3° F.) was essentially negative. Brucellergin skin tests were positive. He had serum agglutinins 1 to 160 and an opsonocytophagic index of 37. W. B. C. 4300, with relative lymphocytosis. On the third hospital day he developed sore throat and slight generalized enlargement of the lymph nodes. His W. B. C. rose to 18,000 with 26% monocytes, and his heterophile antibody titer was 1 to 1024. Two weeks after recovery and discharge he returned, complaining again of fever, general malaise, and slight diarrhea. Physical examination was essentially negative, and the W. B. C. was 4800. *Salmonella schottmülleri* was isolated from the stools, and he made an uneventful recovery. This is an example of infectious mononucleosis, followed by paratyphoid fever, which could have been diagnosed incorrectly Brucellosis by the laboratory findings.

No. 92654. A white male, aged 43 years, entered the hospital complaining of general lassitude, weakness, and low-grade fever of 10 months' duration. Brucellergin skin tests were positive, agglutination positive for *Brucella* in a dilution of 1 to 80, and the opsonocytophagic index was 43. Proctoscopic examination revealed a small rectal polyp which was removed. Pathologic study revealed an adenocarcinoma.

No. 77127. A 26-year-old white male entered the hospital complaining of intermittent fever for 11 months. Brucellergin skin tests were negative; there were no demonstrable agglutinins and his opsonocytophagic index was 0. There was generalized enlargement of the lymph nodes. One of these was removed, and *Brucella*, variety *suis*, was isolated. This patient subsequently died, and the diagnosis of Brucellosis was proven at necropsy. This instance of chronic Brucellosis would not have been correctly diagnosed had complete dependence been placed in the usual diagnostic procedures.

No. 50291. A 31-year-old white male entered the hospital complaining of fever, chills, and a sore throat for the past 48 hours. Physical examination revealed unusual ulcerations in the mouth and pharynx. Skin tests with Brucellergin were negative; there were no agglutinins and the opsonocytophagic index was 0. *Brucella*, variety *melitensis*, was isolated from the blood stream on the second hospital day. He responded well to immune sera and after 9 days developed an agglutinin titer of 1 to 320. His opsonocytophagic index was then 92. The Brucellergin skin test is still negative after 4 months.

Summary and Conclusions. 1. There appears to be a direct relation between raw milk consumption and skin reaction to brucellergin.

2. Skin tests are not without danger, since severe local and systemic reactions are not infrequent.

3. There appears to be little correlation between skin reactivity and measurable antibody content of the serum.

4. Endermic injection of brucellergin will cause a definite increase of circulating antibodies in allergic patients.

5. Brucellergin followed by typhoid vaccine will cause a greater and more prolonged increase of circulating antibodies than brucellergin alone.

6. Any febrile reaction will cause an increase of circulating antibodies.

7. In survey work, a better immunologic picture is obtained by measuring the antibodies at the height of the antibody response to brucellergin.

8. Negative skin tests, agglutinins and opsonocytophagic reactions do not rule out the possibility of *Brucella* infection.

9. Positive skin tests, low agglutinins and a moderate opsonocytophagic reaction, even when accompanied by suggestive signs and symptoms, do not prove the diagnosis of brucellosis.

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SHORT WAVE AND ULTRA SHORT WAVE DIATHERMY.

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By the term short wave diathermy or short wave therapy is meant the therapeutic use of an electric or electromagnetic field produced by high frequency currents of a wave length ranging from 3 to 30 meters. To waves from 3 to 10 meters in length the term ultra short waves is often applied. The designation short wave therapy is rather unfortunate as it may occasion confusion with short wave radiations such as ultra violet and Roentgen rays. Our present knowledge began with d'Arsonval's⁴ discovery that high frequency currents can be applied to the human body without danger of shock and with the disappearance of muscular irritability with increasing frequency. It was also d'Arsonval who first attempted to use them in treatment. Increased output of energy was achieved by improvements in construction of machines. The technical foundation of short wave therapy was laid chiefly by Esau⁸ and Schereschewsky.^{27b} The first demonstration of the usefulness of these short waves in treatment was made by Schliephake^{28b} who exposed a painful furuncle on his own nose to their action with the result that the pain was at once allayed and the inflammation quickly subsided.

An increasingly large number of publications have appeared since

Schliephake^{28a} published his first papers in 1928. Books in German, French, Italian and English with contributions in medical journals totaling, according to de Cholnoky,^{5a} approximately 750 publications indicate the growing interest in this subject. Unfortunately, many communications display an unjustifiable optimism regarding the value of short wave therapy. This is usually the result of drawing conclusions from an inadequate number of observations, and of attributing all recoveries to the treatment employed.

To enumerate all diseases and symptoms for which short wave therapy has been regarded of value would almost cover the whole field of medicine.

There are, however, conditions which make it difficult to evaluate the results of short wave therapy even for those who are working in this field. First of all there is no method available for measuring the amount of energy absorbed by the part or parts of the body under treatment. Recently, Mittelmann²² demonstrated a new device which at least enables one to measure the amount of energy absorbed by the whole body, but it still leaves unsolved the problem of how much energy a particular area of tissue is getting. The inability to measure the output or the energy utilized makes difficult the comparison of the results obtained by different authors. Other obstacles are that differences in the size of electrodes, their application, their distance from the part of the body treated, the length of cables and the "tuning in" of the machine, which alter the output or the configuration of the condenser field. These difficulties are further increased by the fact that machines of different size and construction with varying outputs of power, with and without the condenser field, are in use in this country and in Europe. When improvement consists of the removal of subjective symptoms it is often difficult to determine whether this is due to the action of the short waves or to the influence of suggestion, always an important factor when a new treatment is given, and especially so when it consists of radiations generated by an impressive looking machine.

Haase and Schliephake,¹¹ and Liebesny, Wertheim and Scholz²⁰ concluded on the basis of numerous experiments that short waves have a specific bactericidal effect in addition to their thermal action. Schereschewsky and Felton,^{27a} in unpublished work and, more recently, Ruete²⁶ and a number of other investigators (cited by Krusen¹⁷) were unable to demonstrate any specific action on bacteria. Experiments by Pflomm²³ seemed to prove that the short wave produced specific action on the circulation of blood through the capillaries and on the autonomic nervous system, but recently his conclusions have been overthrown by Weiss, Pick and Tomberg²⁹ who show the changes produced in the blood vessels are due entirely to the thermic effects. It can be definitely asserted that heat production in the tissues is the only action of short waves that has been demonstrated.

The chief advantage of the short waves over the much longer waves employed in conventional diathermy is that they penetrate the tissues much more, and generate higher temperatures at a considerable depth below the surface of the body.

Even the so-called "athermic therapy," recently employed and endorsed by the Austrian authors Liebesny^{19d} and Weissenberg,³⁰ can probably be explained as due to the production of a mild, insensible heat, the effect of which is possibly more favorable in certain conditions than strong heat. If the current is so weak as to be really "athermic" it probably has no therapeutic action at all. Hasche¹² has been able to study separately the "thermic" and the "athermic" short wave field and concludes that the latter has no bactericidal power and no physiological effect.

During the past 4 years the effect of treatment with ultra short and short waves has been observed at the Boston Dispensary on a variety of pathologic conditions. It is hoped that an analysis of the observations made on more than 600 patients treated will be of help in determining the value of short wave therapy in some diseases, its lack of value in others, and its effectiveness compared with other forms of treatment.

Methods. Three different types of machines have been used: First, a spark-gap apparatus generating a band of waves ranging in length from about 10 to 30 meters. With this, rubber electrodes applied to the skin were used. Second, an apparatus with two large vacuum tubes. This was the most powerful generator obtainable. It has an output which reaches 800 watts on a 15-meter wave, 600 watts on a 6-meter and 300 watts on a 4-meter wave. With it, wave lengths from 3.5 to 7 meters may be used and also a fixed wave length of 15 meters. As this machine was the same as that employed by Schliephake,^{28d} Liebesny^{19c} and other European workers, failure to confirm the curative effect obtained by them in some diseases cannot be attributed to any deficiency in the equipment employed. Third, a small vacuum tube machine with an output of 225 watts on a wave length of 6 meters.

The glass shoe electrodes designed by Schliephake have been found most satisfactory as with them it is possible to vary easily and rather accurately the distance of the electrode from the surface of the skin. With them the application of short waves can be supervised better than with any other form of electrodes. Less danger of burning attends their use, as an air gap is left between the electrodes and the skin. Especially designed electrodes for rectum, vagina and axilla are available.

Important variations in the thermal effects at various distances below the surface of the skin depend on the distance of the electrodes from the skin and the arrangement of the two electrodes to form the condenser field.

Different wave lengths, namely 4, 6, 7, and 15 meters, have been used and the results compared to determine if there exists an optimum wave length for different conditions. This attempt has failed and it is impossible to state that a certain wave length is the best in the treatment of a particular disease. Knowing that the output of power decreases when the very short waves are employed, it was found in accordance with the experience of others that, in conditions where no strong heat effect was desired, low wave lengths were usually to be preferred.

As, theoretically at least, ultra short waves should generate more heat at a greater depth than do the longer waves, we used the 4 or 6 meter in treating deep seated lesions, such as lung abscesses and empyema. Coulter and Carter² and Coulter and Osborne³ have shown experimentally that longer wave lengths raise the temperature of the deeper tissue to as high a point as the 6-meter wave. Although they used machines with less output than ours, it is possible the same result would have been obtained with the equipment and technique we employed. In certain cases in our experience on patients where a high degree of heat was important, it seemed as if better results were obtained with a 15-meter wave than with a 4 or 6 meter. This can probably be explained as due to the greater electrical energy when the 15-meter wave length is used.

The following case illustrates the injurious effect of an excess of heat. The patient was a 46-year-old male who had recurrent furuncles. On 3 occasions cure was quickly effected by 2 treatments, each lasting 10 minutes. When he returned a fourth time, after an interval of many months, the attempt was made to cure a small furuncle that had appeared on his wrist by a single treatment of 20 minutes' duration. The result was necrosis of the furuncle and the surrounding tissues. Ulceration occurred and delay in healing.

When a definite heat effect was sought, the duration of the treatment was usually 20 minutes. On the other hand, if a mild hyperemia was desired, a treatment lasting only 5 or 10 minutes was given. The initial treatment in many cases was limited to 10 minutes even when a rather intense generation of heat in deeper tissues seemed desirable. One treatment a day was the rule; occasionally in dealing with severe inflammatory lesions a second treatment was given the same day. Rarely an unfavorable reaction occurred, either in the form of an increase of pain, faintness or evidence of vasomotor weakness. When this took place treatment was omitted the following day. Thereafter the treatments were resumed without untoward symptoms.

As Rausch²⁵ and de Cholnoky^{5a} have observed, a slight fall of blood pressure and increase of blood sugar occurs during short wave treatment. These transitory effects, however, did not interfere with the treatment of our arteriosclerotic patients. Although age is no contraindication for short wave treatment, more care is necessary in elderly patients regarding duration and intensity of treatment since they are more liable to the unfavorable reaction just mentioned. It has never been necessary, however, to abandon the treatments. There is no difficulty in dealing with the young, as children react especially well. Our youngest patient, a baby of 6 months with a large abscess covering one-third of its back, was well on the road to recovery within a week.

To have a check on the results, the dispensary patients were examined in the various clinics from which they were referred, not only before treatment, but during its progress and at its close. Helpful in judging results in infections were reduction in the leukocyte count and especially in the sedimentation rate.

Excepting a slight burn in one case, already mentioned, there were no untoward results. To avoid burns and other injurious effects, short wave therapy was refused to patients presenting any of the following conditions; (1) impaired sensation of the skin; (2) arterial

or venous occlusion of peripheral vessels with evident damage to the tissues; (3) advanced stages of diabetes mellitus unless under strict hospital supervision; (4) arteriosclerosis with marked hypertension.

Pregnancy is not a contraindication and studies have shown there is no danger of injuring the fetus (Raab and Hofmann²⁴). During menstruation, short wave treatments should be discontinued since there may be increased flowing as a result of hyperemia of the uterus produced by the short wave.

Results. *Furuncles, Carbuncles and Abscesses.* Schliephake has shown that acute suppurative lesions of the skin and subcutaneous tissues are quickly healed by short waves. He states in the latest edition of his book^{28c} that he treated over 500 cases of furunculosis with only one failure. In all the other cases, healing took place in a very short time while patients continued at work. Very favorable results were also obtained by Liebesny^{19a} of Vienna. "In about 500 acute inflammatory lesions" Liebesny observed only 1 case in which a definite exacerbation occurred following ultra short wave treatment and 1 case with delayed healing. He had striking success in treating that serious condition, furunculosis of the face, reporting only 2 deaths in 86 cases. In this country, excellent results in a large series of cases have been reported by Egan⁷. de Chohnoky^{5c} cured 57 cases of furunculosis, and only in 1 case was an incision made.

The least enthusiastic opinion we have seen regarding the treatment of furuncles and carbuncles with the short wave from one who has had experience with adequate apparatus and had used proper technique is that of Kowarschik.^{16a} He admits its superiority to other methods of applying heat; first, as the short wave acts at a greater depth and, secondly, it causes no maceration of the surrounding tissues which favors the spread of the inflammatory process, as do moist compresses and poultices. For treating simple infections he thinks the rapidity of cure does not compensate for the expense. He insists that no effective method is absolutely harmless and points out the danger of causing a spread of the infection if an improper technique is used as Haas and Lob¹⁰ found. Kowarschik^{16a} states the undoubted truth that every severe infection of the subcutaneous tissues should be under the supervision of an experienced surgeon, in addition to the short wave specialist, and the former should decide when short wave treatment should be interrupted and an operation performed.

There is a general agreement among those who have had experience with short wave therapy that pain in the infected areas quickly disappears. Usually one or two short exposures are sufficient to give speedy relief from tension and throbbing. If treatment is begun in the early infiltrative stage, regression may occur. In more advanced cases, especially where pus has formed, spontaneous rupture of the abscess usually takes place.

This form of treatment has a great advantage over other procedures in dealing with furuncles of the upper lip, nose and cheeks. Operative procedures have yielded a shockingly high mortality. The best surgical practice of today in dealing with these dangerous lesions is reflected in the recent paper by Maes²¹ on this subject, who advises complete rest to the parts. Talking and chewing should be forbidden when the lip is involved. In the statistics of Küttner-Dittrich,¹⁸ the mortality of furuncles of the upper lip was 19%, while in Koslin's¹⁵ series it was 30%. Since direct local application of heat to the edematous tissues is difficult, the employment of the glass shoe electrodes with their air gap between skin and electrode is especially advantageous.

We have treated 51 cases of furuncles. Eight of these involved the upper lip, nose or cheek. One of these was a severe infection. Swelling of the nose with edema of the right half of the upper lip and discharge from the right nostril developed. The next day he was given a short wave treatment. During the following night, edema of the lip increased and he had difficulty in breathing. The temperature rose to 100.2°. He was given a second treatment and put to bed. He recovered with only those two treatments. Four of the 51 are put down as failures as they abandoned treatment, but it is possible they felt so little discomfort that they did not consider further treatment necessary. In the other 47, there was rapid improvement and healing. There was no fatality. The duration of a single treatment was usually 10 minutes but occasionally two treatments were given daily.

In agreement with Schliephake, Liebesny and others, we have obtained good results in the treatment of carbuncles. The treatment failed in 2 cases. One of these, a 60-year-old man with severe diabetes, had septicemia when treatment of an extensive carbuncle started. The other, a large carbuncle of the back of the neck, was incised after 3 treatments by a surgeon who preferred the knife to conservative treatment. Healing was speedy. In 9 of our 11 cases, there was a rapid localization of the inflammation, with the formation of pus in one area, decrease of pain, and spontaneous rupture with good drainage. In our series, the average duration of treatment was 12 days; average number of treatments, 9. In every one of these 9 cases it was possible to prevent surgical intervention with its large incision, prolonged suppuration, slow healing and unsightly scar formation.

Paronychia, especially its chronic form, responded well to short wave therapy. In 8 of 10 cases with chronic infiltration and continuous drainage of pus which had persisted for from 2 months to a year or longer in spite of a variety of local treatments, improvement followed the use of short wave; suppuration ceased and there was decreased swelling. The other 2 cases were not followed sufficiently long to permit of a definite conclusion. One of these took only 3 treatments, the other only 4. The average number of treat-

ments in those successfully treated was 11. de Cholnoky^{5d} and Egan,⁷ in this country, also obtained good results in this disease with the short waves.

Lymphadenitis. In cases of lymphadenitis of unknown etiology or following the extraction of teeth, our results were poor. In only 3 of 12 cases did the swelling of the lymph nodes subside. In all cases, however, subjective symptoms were relieved, but in 3 of these an incision was necessary.

Arthritis. Good results were obtained in *acute arthritis*. This is in accord with de Cholnoky's conclusion that short wave therapy gives the best results in the acute and subacute inflammations of the joints in which long wave diathermy can be used only with extreme caution and even then with the danger of undesirable reactions. In 7 patients with *gonorrheal arthritis*, there was rapid and marked improvement. Pain subsided speedily. Four were practically cured. Two in whom there was chronic involvement of the joints had less pain but no objective improvement. Our results correspond with those previously reported by many investigators. No other method of treatment is so successful. de Cholnoky, after making a study of the literature, states that the results are uniformly satisfactory.

Fourteen patients with acute infectious arthritis of unknown origin did well. In these the swelling subsided after 3 or 4 treatments and motion was restored after about 2 weeks. Average total duration of treatment was 20 days. Three cases showed no improvement. The effect of treatment was especially striking in the case of recurrent acute arthritis of the right elbow joint in a 55-year-old man. The elbow was greatly swollen and acutely inflamed. A roentgenogram revealed marked destruction and a tumor-like proliferation of the cartilage (chondroma). The blood sedimentation rate was 12 mm. in 1 hour (Westergren) before treatments were started and 3 mm. in 1 hour when discharged. He was treated in 2 attacks. In both there was rapid and complete subsidence of the acute inflammation. Pain ceased after 2 treatments and motion was restored after 4 treatments.

In the treatment of *chronic osteo-arthritis* (hypertrophic arthritis), a disease in which it was thought this new form of treatment would be most beneficial, the reports are conflicting. In the third edition of his textbook, Schliephake^{28f} speaks more reservedly of the benefits of local ultra short wave treatment than in the first edition. In a later publication^{28g} dealing with joint diseases, he recommends short wave electropyræxia when a large joint or multiple joints are involved and, in addition, the use of drugs and other therapeutic methods. In the first edition of his textbook, Schliephake^{28c} gives the impression that practically all patients are benefited by placing the affected joints in a condenser field, but in his most recent paper^{28g} he states that often no improvement is obtained by local treatment.

Kowarschik¹⁶⁶ has obtained good results with short wave therapy but not essentially better than with the older forms of thermotherapy. Horsch¹³ treated a large series of cases of hypertrophic arthritis and obtained improvement in only 23%. On the other hand, de Cholnoky⁵⁶ treated 35 cases with only a few failures. Usually after a few treatments pain was diminished, swelling decreased and functions improved.

Fourteen of our 44 cases of hypertrophic arthritis showed some slight improvement. Many of these had marked changes in the joints and bones and therefore less pain, and better motion was all that could be expected.

Rheumatoid Arthritis. Contrary to the experience of most investigators, we had more success in atrophic than in hypertrophic arthritis. Among 38 patients with rheumatoid arthritis, in 20 the pain was lessened and better function of the joint obtained. In 3 of 7 cases of *spondylitis ankylopoietica* some improvement was noted. An average number of 10 treatments was given these patients.

Rhinitis. Short wave therapy has been given to a number of cases of *acute rhinitis* occurring in members of the medical staff and employees of the hospital and dispensary. A quick subsidence of symptoms was observed in every case after an early short wave treatment, but there was a recurrence in some cases within a few hours.

Vasomotor rhinitis due to allergic conditions did not subside during short wave treatment.

Empyema of the Accessory Nasal Sinuses. The beneficial effect of short wave therapy in *acute and chronic inflammation of the accessory nasal sinuses* has been as striking in our experience as in that of earlier workers in this field. All are agreed as to its value. Often occlusion of the nasal passages is relieved after the first treatment. In cases that respond favorably, the discharge quickly lessens and loses its purulent character. Even in cases of long duration the discharge may entirely disappear or be reduced to an insignificant amount. Recurrence of symptoms within a few months often occurs. Many of our patients had been previously subjected to various operations. A number of patients upon whom operations had been advised were freed from their symptoms by short wave treatment. In our series of 80 cases, no effect on the nasal discharge was obtained in 26, while in 42 the discharge was lessened or lost its purulent character or ceased. The subjective symptoms, headache, sense of fullness, and so on, disappeared under treatment in all but 11 cases. One patient with severe chronic sinusitis failed to improve when treated in a 4-meter condenser field. A year later he obtained signal benefit from a second course of treatments in which the 6-meter wave was used. The best results have been obtained in those cases in which the maxillary antra were involved. The average duration of treatment was 3 weeks. The number of

treatments usually ranged from 7 to 18. The length of exposure to the short wave was generally 15 to 20 minutes.

Prostatic Disease. In 7 cases of *hypertrophy of the prostate* and 3 of *chronic prostatitis* in which frequency of urination and pain were outstanding symptoms, there was marked relief obtained from ultra short wave radiation. Usually during treatment urination decreased from many times a day to the normal number. After treatment was discontinued the symptoms recurred.

Bursitis. Of 72 patients with *subdeltoid* or *subacromial bursitis* 35 obtained symptomatic relief from short wave therapy, and 9 were completely cured. Roentgenograms showed a diminution of calcified deposits in 3 patients. Prolonged treatment was required as a rule, which in a few cases lasted 2 months. Occasionally, a reaction followed the first 2 or 3 treatments.

Neuritis and Neuralgia. In 1 case of severe acute sciatica which was treated in our hospital there was rapid cessation of pain and no recurrence after treatment. Ambulatory patients with sciatica on the whole did not do well. In some patients there was a definite hypersensitivity even to slight heat. In contrast to the favorable results obtained by de Chohnoky we failed to obtain improvement in 3 cases of trigeminal neuralgia and 3 cases of occipital neuralgia.

Myositis and Myalgia. In painful affections of the muscles of unknown etiology lessening of pain and restoration of function usually took place rapidly.

Ulcerations Following Radium Therapy. Three cases have been successfully treated. In the first patient a year after a cancer of the upper lip had been removed by radium an ulcer formed in the poorly vascularized tissues. As it showed no tendency to heal excision was considered, but it was decided to try first the effect of short wave. When treatment was instituted, the lesion measured 15 mm. by 9 mm. surrounded by an erythematous area of equal width. There was less tenderness after 2 treatments. After 3 treatments the size of the ulcerated area was 10 by 8 mm. After 5, it measured only 8 by 4 mm. Treatment was then discontinued. A few days later, healing was completed.

After radium treatment of 2 large cancers of the tongue, deep extensive ulcers formed which showed no tendency to heal. In both there were sloughing ulcers involving the whole left border of the tongue. Daily treatments of 20 minutes' duration were given. The electrodes were placed on each side of the mouth at about 3 cm. distant from the cheek. A wave length of 6 meters was used. In 1 case, sloughing and pain decreased after a few treatments and healing was completed in 2 months. In the second case, the ulcer was treated by various means for over a year without success. Pain was constant and severe. Eighteen short wave treatments were given before healing began. A month later only slight ulceration remained. After healing the tongue was smooth and clean but a deep wedge-like defect marked the site of the ulcer.

Lung Abscess. It was the remarkable results reported by Schliephake in the treatment of this serious and often fatal disease that was the chief reason for the importation of the expensive powerful short wave apparatus which he employed. It seemed reasonable that if we hoped to duplicate his results we should possess the same equipment and use the same technique. Schliephake^{28d} reported 9 cases of lung abscess, all of which were cured by short wave. The evidence from case histories was supported by roentgenograms. Liebesny^{19b} claimed 4 cases were cured among 6 treated. The 2 failures were attributed to faulty technique. Fiandaca⁹ reported the successful treatment of 10 of 12 cases, but there was no report of the condition of the patients after leaving the hospital. Cignolini¹ treated 7 cases with varying results, "*esito vario*," and reported 2 cases treated by colleagues that were cured. Izar¹⁴ treated 3 cases of lung abscess 20 to 40 minutes daily for a month, using 4, 8 and 15-meter waves, with no result. Further confirmation of the value of short wave in the treatment of lung abscess was apparently furnished in a recent report by Dieker⁶ from the Heidelberg medical clinic of 15 recoveries of 16 cases treated. This paper is illustrated with Roentgen ray evidence of cures effected. In spite of the fact that all the reports in the literature in which the Ultra-Pandoras was used were favorable, we, using the same machine, have not cured a single case of lung abscess among 8 treated. In 1 case, the clinical results were striking. The Roentgen ray, however, showed a persistence of the abscess although much diminished in size. Within a year symptoms returned and at operation a large abscess was found.

In the treatment of bronchiectasis, bronchial asthma and chronic bronchitis, we have seen no definite improvement.

We have had only failures in the 1 or 2 cases treated of the following diseases: multiple sclerosis, syphilis of the central nervous system, subacute bacterial endocarditis and osteomyelitis.

Two of our 3 cases of Raynaud's disease were treated without success. Even a mild treatment increased pain. Both cases showed definite organic changes in the fingers. In the third patient, the relation of the spastic attacks to emotional disturbances was undoubted. Although gangliectomy had been advised in this case, a good result was obtained by short wave therapy. As the psychic element was important in the causation of symptoms, it may have been the chief factor in the therapeutic success.

Summary. In our experience, short wave diathermy hastened cure in acute subcutaneous infections (furuncle, carbuncle, abscess). Good results, often cure, were obtained in certain forms of acute arthritis, especially that of gonorrheal origin. Acute and chronic bursitis were often favorably influenced. Symptomatic relief occurred in about half of the cases of rheumatoid arthritis and in exacerbations of chronic sinusitis.

In the treatment of lung abscess and bronchiectasis, no favorable effect has been obtained by us.

In conclusion, the statement is warranted that short wave therapy is safe and easy of application, and of definite, although limited, therapeutic value.

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THE SIGNIFICANCE OF SMALL AND ABSENT INITIAL POSITIVE DEFLECTIONS IN THE CHEST LEAD.

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In the past few years there have been numerous articles dealing with the precordial leads of the electrocardiogram. These studies, both clinical and experimental, have been carried out with a variety

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of techniques. Recently¹ an attempt has been made to standardize the precordial leads used in clinical electrocardiography, especially for routine work where a single precordial lead is used. This is a distinct step forward and will eliminate much confusion which has existed in the past. The whole matter is not finally settled and the recommendations for standardization were not intended to discourage further investigative work.

The normals have been quite well defined and certain facts have been established in relation to the various components of the precordial electrocardiogram. The following changes have been frequently observed and certain clinical associations have been noted (the precordial electrode being placed on the area of the cardiac apex beat and the other electrode on the left infrascapular area or left leg).

1. The initial positive deflection of the *QRS* complex (*Q* wave of old technique, *R* wave of new technique) is practically never absent in normal hearts.^{5,7,9a,10}

2. Absence of the initial positive deflection is most often seen following a recent or old myocardial infarction at the apex of the left ventricle anteriorly.^{2,11a,b,12} A few other conditions, nearly all organic heart disease, may cause absence of this deflection.

3. A small initial positive deflection (less than 2 mm.) is frequently seen in various types of organic heart disease.^{6,8} It is a less valuable sign than an absent initial deflection and probably is seen occasionally in normal hearts. In many patients the height of the initial deflection varies greatly with the position of the precordial electrode. In these cases the point of application of the electrode may be responsible for an abnormally small initial deflection.⁴

4. Changes in the *T* waves of the precordial lead are usually associated with changes in the same wave in Lead I. Occasionally an abnormal *T* wave in the chest lead is the only significant change present in the electrocardiogram.³ A normal *T* wave is not infrequent in the precordial lead with inversion of the *T* waves in one or more of the limb leads, especially Leads II and III. The position of the precordial electrode may alter greatly the size and contour of the *T* wave in this lead.^{9b}

Important changes in the *QRS* complex of the precordial lead (absent or small initial positive deflection) may be present with little or no change in the *QRS* or *T* waves of the limb leads. There is considerable evidence to the effect that these changes, when present, tend to be more permanent in nature than *T* wave abnormalities. For this reason they may remain as residual findings (especially after myocardial infarction), when the *T*-wave alterations have returned to normal. It should be remembered that severe heart damage may be present with little or no alteration in the precordial lead and that the significance of abnormal findings in the limb leads is not altered by a normal Lead IV.

It seemed worth while to us to analyze the electrocardiograms in our files in which an absent or small initial positive deflection was noted in the precordial lead. The correlation of these changes with abnormalities in the limb leads and *T*-wave changes in both the precordial and limb leads seemed important. The clinical histories of these selected cases were then studied in order to determine the presence or absence of heart disease and the etiologic and anatomic diagnoses.

For the past 3 years at the Pennsylvania Hospital a precordial lead has been recorded routinely on all adults on whom an electrocardiogram was taken. Lead V of Wolferth and Wood^{11b} (R.A. electrode on the cardiac apex and L.L. electrode on the left leg) was used during most of this period. For 2 years prior to this, Leads IV, V and VI (Wolferth and Wood) were taken in cases in which coronary disease was suspected. Several months prior to the completion of this study, the routine precordial lead was changed to Lead IV R (L.A. electrode on apex and R.A. electrode on right arm). This last lead is one of those recently recommended for routine use by the American Heart Association.¹ It has the advantage of being comparable to the limb leads and is essentially the inverted mirror image of the old chest lead. The records from this study were taken from approximately 10,000 consecutive records during the above period. There were records from 102 patients with an absent initial positive deflection in the precordial lead (*Q* wave of the old technique and *R* wave of new), and from 46 patients with a small initial positive deflection (less than 2 mm.) in the precordial lead.

Technique. The precordial electrode used during most of the study was a German silver electrode measuring approximately 4 by 6 cm. This was changed to a circular electrode 3 cm. in diameter during the last few months of the observations. The electrode was placed as nearly as possible on the cardiac apex as determined by palpation and percussion. In patients with very large hearts the electrode was placed somewhat medial to the apex and was seldom placed outside the anterior axillary line. (Observations on a number of patients with greatly enlarged hearts led us to believe that it was unwise to place the precordial electrode on or "just outside" the apex beat in these cases, as has been recommended for routine use. The results of a special study on a total of 67 patients with normal and abnormal hearts, using six precordial areas for the exploring electrode and the right arm, left arm and left leg, respectively, as the indifferent electrode, will be reported in a separate paper.⁴) The indifferent electrode was placed on the left leg during most of this study. The use of the right arm for application of the indifferent electrode (Lead IV R) was found to be as satisfactory and as a matter of convenience was used in the latter part of the study.

Analysis of Cases With an Absent Initial Positive Deflection. There were 102 patients in this series with an absent initial positive deflection. A total of 260 records were taken on these patients. Fifty-three of these cases had 2 or more records. In 49 cases only

1 record was obtained. Of the group with only 1 record, 23 had the electrocardiographic pattern of a recent myocardial infarction at the time the examination was made. A total of 68 patients (67%) had clinical and electrocardiographic evidence of a recent or an old myocardial infarction (Figs. 1 and 2). There were 45 males and 23 females. In all of these patients the location of the infarct as determined by the electrocardiographic pattern was anterior, or both anterior and posterior. Two of the patients had had an old anterior and a more recent posterior infarction. In 1 patient the acute infarct was probably both anterior and posterior, mainly the former, as determined by the electrocardiographic pattern.^{11c} In all of the fatal cases in which postmortem examination was done, the location of the infarct or scar was found to correspond to the area predicted by the electrocardiogram. The youngest of these patients was a male of 39 years, and 58 patients (85%) were between the ages of 40 and 70 years. In 5 of these patients (7.3%) with coronary occlusion, the only significant change in the electrocardiogram, at the time of this analysis, was in the precordial lead. In 11 patients of this group (16%), the main electrocardiographic change was in the precordial lead. Some of these were cases in which the occlusion had occurred several months or years previously, and in many, other abnormalities may have been present in the limb leads during the acute stages. A correlation of the *T*-wave changes in Leads I and IV is of interest and is shown in Table 1. In only 2 cases were the *T* waves normal in both of these leads. In 55 cases the *T* waves were abnormal in both of these leads.*

There were 34 patients in the group with absent initial positive deflection in the chest lead (33%) in which there was no clinical history or findings suggestive of myocardial infarction. Nineteen of these patients were males and 15 females. The youngest patient was a woman of 38 years, and 28 of the total (82%) were between the ages of 40 and 70 years. In 5 of this group (14%) the absent initial positive deflection was the only abnormality in the electrocardiogram. In 10 other patients (29%) the main change in the electrocardiogram was the absent *Q* or *R* wave. This was nearly double the per cent of cases in which the entire or main abnormality was seen in the precordial lead in the patients with myocardial infarction. A comparison of the abnormal *T* waves in Leads I and IV is of interest also in the patients without infarction. In this group the *T* waves were normal in both of these leads in 11 cases. They were both abnormal in only 14 of the 34 cases, and the *T* waves were much more frequently abnormal in the first lead alone than in the precordial lead alone (Table 1).

The etiologic diagnoses were determined from the clinical records and from postmortem studies where such information was available.

* A *T* wave was considered abnormal when it was inverted or diphasic or flat, if digitalis had not been given.

Of the 102 cases, 95 (93%) had arteriosclerotic (coronary) heart disease; 50 of these also had hypertension, and 3 hypertension alone. Six patients had luetic aortitis. This was confirmed at postmortem in 4 of these 6 cases, and in 2 cases there was also myocardial infarction due to the closure of the coronary orifices. Two of the cases with aortitis were also included in the arteriosclerotic group.

TABLE 1.—A COMPARISON OF THE T-WAVE CHANGES IN LEADS I AND IV IN 102 CASES WITH AN ABSENT INITIAL POSITIVE DEFLECTION IN THE PRECORDIAL LEAD.

	T 1 and T 4 abnormal.	T 1 abnormal T 4 normal.	T 1 normal T 4 abnormal.	T 1 and T 4 normal.
68 cases with myocardial infarction	55 (81%)	6 (9%)	5 (7%)	2 (3%)
34 cases with no infarction	14 (41%)	10 (29%)	0	10 (30%)

Analysis of Cases With a Small Initial Positive Deflection. There were 46 patients with a small initial positive deflection in the precordial lead (a Q or R wave of 2 mm. or less was regarded as a "small" initial positive deflection) (Fig. 3, B). A total of 85 records were obtained on these patients. In 26 patients 2 or more records were taken. In 20 patients only one electrocardiogram was available. In those cases with several records, it was not uncommon to find a record with the initial positive deflection of normal amplitude. In most of these cases it was felt the variation was the result of a difference in the position of the precordial electrode rather than any improvement or change in the cardiac status (Fig. 3, A). Further evidence that this was a technical phenomenon was suggested by the fact that some cases with several records would have a normal precordial lead interposed between 2 records with a small initial positive deflection or *vice versa*. Such cases were not included in this series, but were a further stimulus to investigation of the size of the initial positive deflection, using multiple precordial leads in normal and diseased hearts. We are in agreement with Master *et al.*⁸ that a correlation of the height of the initial deflection with the height of the second wave (S wave of the new technique, R wave of the old technique) is desirable. If the second deflection is less than 10 mm. in amplitude the small initial positive deflection is often of no significance and will often be found within the limits of normal on subsequent records with greater amplitude. Cases of this type were not included in this study.

There were 28 females and 18 males in the group with small initial positive deflection. This was in contrast to the absent initial positive deflection group where the males were nearly twice as numerous as the females. Twelve of this group of 46 were below 40 years, while only 2 of the other much larger group were below this age. There were 28 patients (60%) between the ages of 40 and 70 years.

The etiologic diagnoses, as determined largely from clinical study, in the group of cases with *small* initial positive deflections in the precordial lead were somewhat comparable to the larger group in which the initial deflection was *absent*. In 28 patients (61%), a diagnosis of arteriosclerotic (coronary) heart disease was made; 15 of these also had hypertension; 6 (13% of the total) had probably had a previous myocardial infarction (anterior) as determined by the clinical history or previous electrocardiograms, or both (Fig. 4, B). One patient had hypertension with probably no significant coronary disease; 7 patients had rheumatic heart disease and in 5 instances the etiologic agent was syphilis. Four cases had normal hearts clinically, although 1 was abnormally placed because of dorsal scoliosis. This is in contrast to the larger group of cases with an *absent* initial positive deflection in which cardiovascular disease was present in every case (Table 2).

TABLE 2.—A COMPARISON OF THE *T*-WAVE CHANGES IN LEADS I AND IV IN 46 CASES WITH A SMALL INITIAL POSITIVE DEFLECTION IN THE PRECORDIAL LEAD, AND THE ETIOLOGIC FACTORS CONCERNED IN EACH GROUP.

Etiology.	<i>T</i> 1 and <i>T</i> 4 abnormal.	<i>T</i> 1 abnormal <i>T</i> 4 normal.	<i>T</i> 1 normal <i>T</i> 4 abnormal.	<i>T</i> 1 and <i>T</i> 4 normal
Arteriosclerosis	5	1	0	7
Arter. and hyper.	4	6	1	4
Hypertension	0	0	0	1
Rheumatic fever	3	1	1	2
Syphilis	3	0	1	1
Hyperthyroidism	1	0	0	0
Normal	0	0	0	4
Total cases	16	8	3	19
	(35%)	(17%)	(7%)	(41%)

In 12 patients of this group (26%), the *small* initial positive deflection was the only electrocardiographic abnormality present and in 7 (15%) it was the main abnormality. A comparison of the *T*-wave changes in Leads I and IV, as was done in the *absent* initial positive deflection cases, is of interest. In 19 cases (41%), the *T* waves were normal in both leads. In 16 (35%), the *T* waves were abnormal in both leads. *T* 1 was abnormal and *T* 4 normal in 8 cases (17%), and an abnormal *T* 4 with a normal *T* 1 was found in 3 cases (7%). Table 2 correlates the *T*-wave changes with the clinical diagnoses.

Postmortem Studies. In the group of 102 patients with *absent* initial positive deflections there were 30 deaths and autopsies were done in 17 instances. In 9 cases death seemed attributable to a recent myocardial infarction. This was located anteriorly at or near the apex (in some instances involving the interventricular septum) in 7. In 1 instance, there was an old localized scar at the apex of the left ventricle with a recent infarct posteriorly at the base of the same ventricle (Fig. 4, A). In the other case, there was a similar anterior scar and a recent infarct on the midlateral aspect

September 18 December 22 December 29 January 4 February 18

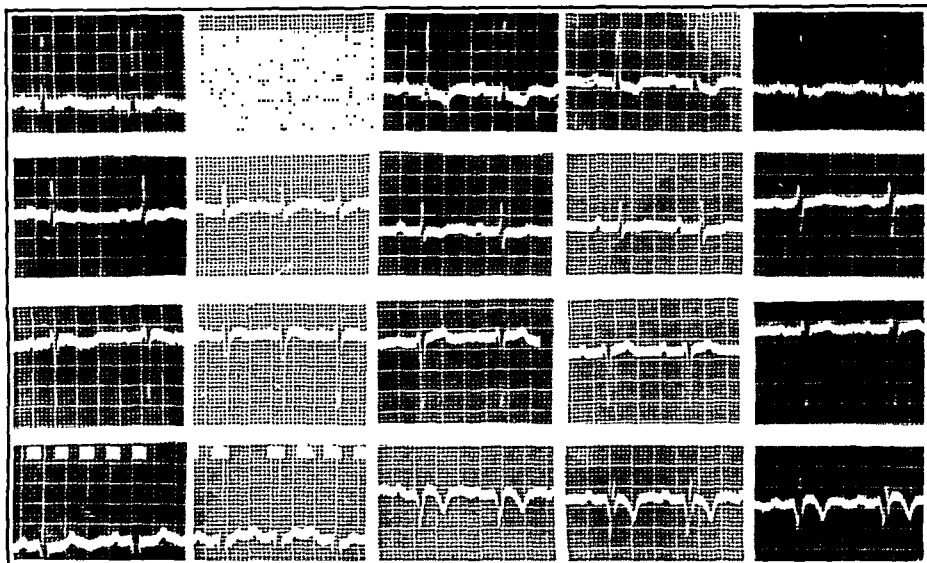


FIG. 1.—Case J. Z., Italian male, aged 68. Arteriosclerotic heart disease with moderate hypertension; Wassermann test positive. Dyspnea on exertion for 3 years, but no precordial pain. Mild cardiac failure present at the time of the record of Sept. 18. Note the relatively slight abnormalities present on this date. Coronary occlusion, Dec. 20. On Dec. 22, the electrocardiogram shows but slight change from the previous record and digitalis had been given for some time prior to this. The tracing of Dec. 29 shows a striking change in the *T* waves in Lead I and the presence of a deep *Q* wave in the precordial lead (IV R) with inversion of the *T* waves in this lead. Feb. 18, the *T* waves in Lead I are beginning to return to normal but the *QRS* and *T* wave changes persist in the precordial lead.

I II III V

A.

B.

C.

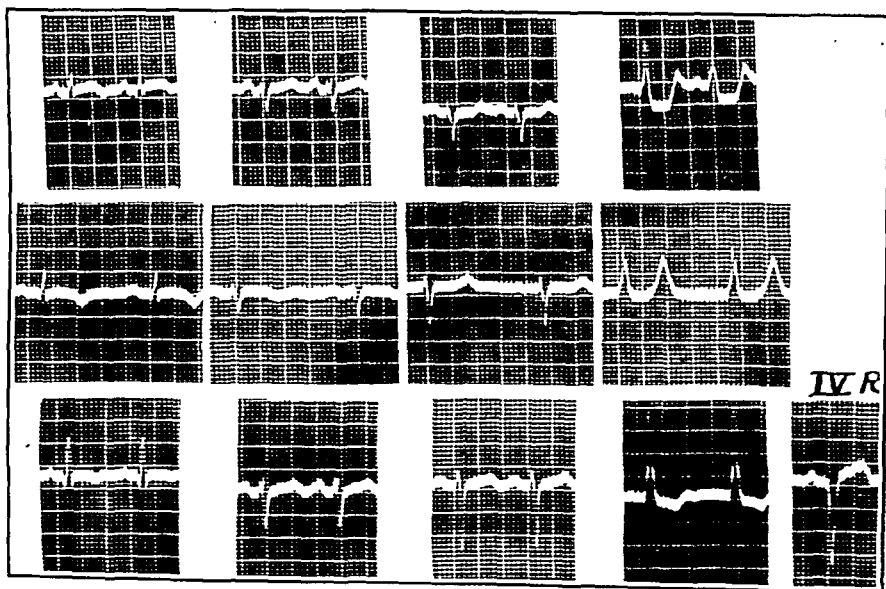


FIG. 2.—Case C. S., colored male laborer, aged 53. Arteriosclerotic heart disease with cardiac enlargement. Typical symptoms of coronary occlusion, Nov. 3, 1936. Gradual improvement but still great limitation of the cardiac reserve to date. A. Nov. 5, 1936. Electrocardiographic pattern of acute anterior myocardial infarction. Chest lead (Lead V of Wollerth and Wood) shows an absence of the initial positive deflection (*Q* wave in this instance) and diphasic *T* waves. B. Dec. 4, 1936. Further *T*-wave changes and persistence of the absent initial deflection in the chest lead. C. July 12, 1938. This record shows much less inversion of the *T* waves in Lead I and return of the *T* waves to normal in the precordial lead. The new chest Lead IV R (apex and right arm) is shown for comparison. Note that the absent initial positive deflection (*Q* wave of the old and *R* wave of the new techniques) has not reappeared in the precordial leads.

I

II

III

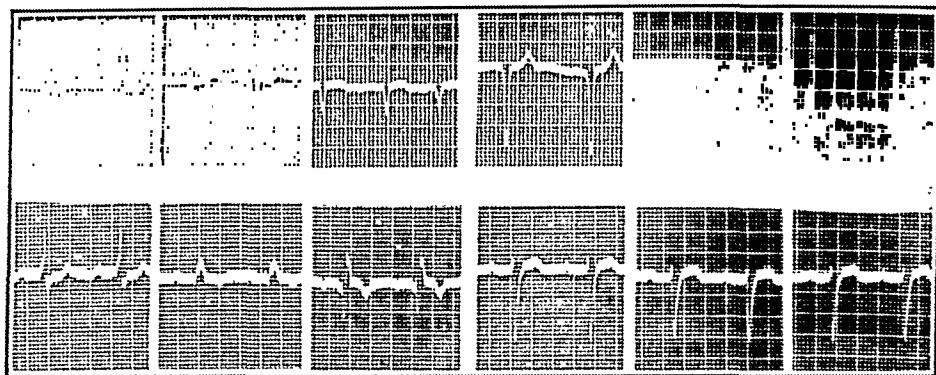
CR₃CR₄CR₅

FIG. 3.—A. Case M. A., white housewife, aged 67. Old rheumatic heart disease with mitral stenosis, arteriosclerosis and hypertension. Marked cardiac enlargement and auricular fibrillation. Digitalized. The limb leads show auricular fibrillation, diphasic *T* waves and left axis deviation. Three precordial leads are shown, using the right arm as the indifferent electrode and the precordial electrode on the parasternal line, CR 3; midclavicular line, CR 4; and the anterior axillary line, CR 5. Note the marked variation in the ventricular complexes in the different positions. The initial positive deflection (*R* wave) is absent in the medial position, within limits of normal at the midclavicular line and large at the lateral position. B. Case M. C., housewife, aged 59. Arteriosclerotic heart disease with cardiac enlargement. History suggestive of old and recent myocardial infarctions. The limb leads show the *QRS* and *T*-wave changes in keeping with a fairly recent posterior infarction. A slight delay in the *A-V* conduction time also is present. The chest leads show little change in the *QRS* complexes in the different positions. The small *R* wave is probably the residual finding of an old anterior myocardial infarction in this instance.

I

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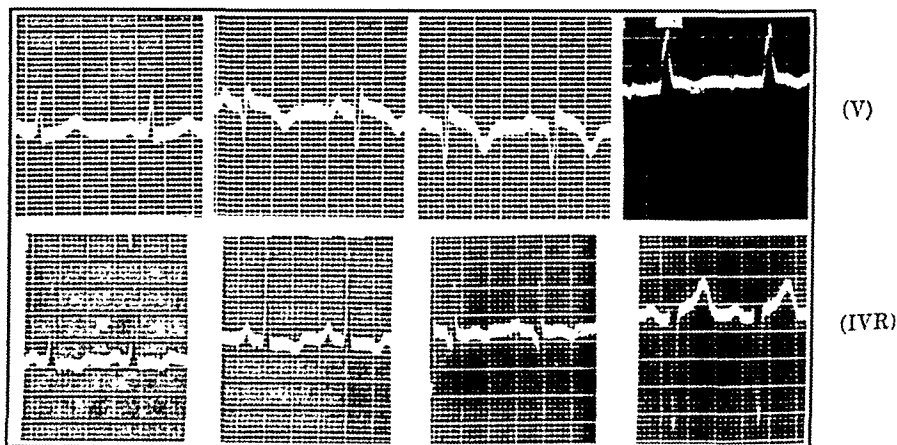


FIG. 4.—A. Case H. R., white male, aged 61. Atypical but severe attack of coronary occlusion followed by the clinical course of myocardial infarction. Similar attack 6 years before with good recovery after a few days in bed. Sudden death on the fifth day after the onset. Note the pattern of acute posterior infarction in the limb leads (third day). The chest lead (Lead V of Wolfarth and Wood), taken the following day, shows an absence of the normal initial positive deflection (*Q* wave) with normal *T* wave. A delay in the *P-R* interval is also present. The diagnosis of recent posterior infarction seemed evident and, on the basis of the chest lead findings (absent initial positive deflection) and the history, a diagnosis of old anterior infarction was made. Postmortem examination proved both to be correct. B. Case E. P., colored housewife, aged 42. Syphilitic aortitis and aortic insufficiency with marked cardiac enlargement. Blood pressure, 190/60. Dyspnea on exertion and some precordial pain. Definite *T* wave changes are present in the limb leads. The chest lead (IV R—new technique) shows a normal *T* wave but a small to absent initial positive deflection (*R* wave). This finding alone is strong evidence that myocardial changes are present.

of the left ventricle with rupture through the ventricular wall and hemopericardium. In 4 of the autopsies a localized scar was found on the anterior surface of the left ventricle near the apex, the result of an old coronary occlusion. The area of infarction or scarring was apparently secondary to coronary thrombosis in all but 1 case where closure of the orifice of the left coronary artery resulted from syphilitic aortitis. Two cases showed coronary sclerosis with diffuse scarring of the left ventricle but no localized lesion. One of these patients died as the result of cardiac failure and the other from cerebral hemorrhage. In the latter case, signs and symptoms of cardiac insufficiency had been present some months before death. Syphilis was the etiologic agent in the 2 final cases. Luetic aortitis with involvement of the aortic valve were present in both instances with cardiac hypertrophy, dilatation and myocardial fibrosis. Death had resulted from cardiac failure. Hypertension had been present in 12 of the 17 cases during life; being present in 8 of the cases with recent or old infarction, in the 2 coronary sclerosis cases without infarction, and in both of the cases with syphilitic aortitis and aortic insufficiency.

There were 8 deaths in the group of 46 patients with a small initial positive deflection in the precordial lead. Postmortem examinations were done in 4 of the cases. In all of these, organic heart disease was found, though in 2 instances death resulted from other causes. The anatomic diagnoses were as follows: Luetic aortitis with cardiac enlargement and myocardial fibrosis; rheumatic heart disease with mitral stenosis and aortic insufficiency and extreme hypertrophy and dilatation (heart weighed 720 gm.); arteriosclerotic heart disease with cardiac enlargement (history of hypertension). The final case showed cardiac enlargement (520 gm.) with diffuse degenerative changes in the myocardium but little gross coronary disease. Clinically, auricular fibrillation was present and death resulted from congestive heart failure in this case.

Discussion. It has been recognized for some time that the initial positive deflection of the precordial lead (*R* wave of new technique and *Q* wave of old technique) is frequently absent following infarction of the anterior wall of the left ventricle. The same is not true of infarction of the lateral and posterior walls of this ventricle. A few cases have been reported in which this wave was absent and apparently no cardiac disease was present. In our series of 102 cases with this finding, however, organic cardiovascular disease was present in every case. The findings compare closely to those of Master *et al.*⁸ in this group, approximately two-thirds of the cases in both series having recent or previous myocardial infarction. The electrocardiographic pattern of all of our cases suggested the area of infarction or scar was anterior or both anterior and posterior. This finding was confirmed in all of the postmortem examinations. We found no instances of typical posterior infarction alone in which

the initial positive deflection was absent. That this wave may be absent in conditions other than myocardial infarction is obvious from analysis of our records and from cases reported by other authors. Our series of cases with this sign were limited nearly entirely to arteriosclerotic (coronary) heart disease excepting a few patients with luetic aortitis. Most of these latter were complicated by hypertension or coronary orifice involvement. The exact cause of absence of the initial positive deflection has not been finally determined and it is probable that several different factors may be involved. All writers agree that anterior infarction is the most frequent cause. Master *et al.*⁸ believe cardiac enlargement or rotation may often be the factor and that even capillary damage (?) (acute nephritis) may occasionally cause absence of this wave. In our cases in which myocardial infarction was not present, myocardial damage secondary to coronary or aortic disease was the usual apparent cause of absence of the initial positive deflection. Cardiac enlargement may also have been a factor in some of these cases. That severe myocardial damage, cardiac enlargement, and even anterior infarction may be present without abnormal changes in the precordial lead is well known and tends to complicate the problem. This fact, however, must be recognized and borne in mind when interpreting electrocardiograms with abnormal findings in the limb leads accompanied by a normal precordial lead.

When the initial positive deflection of the precordial lead is completely absent (if the technique of taking the lead has been correct), it probably rarely returns to normal. In 1 of our cases (proved at postmortem), this wave was still absent 6 years after the occurrence of an anterior infarct (Fig. 4, A). In general, the *QRS* abnormalities in the precordial lead seem to be less susceptible to change (return to normal) than do the *T*-wave changes in this lead.

The presence of a *small* initial positive deflection (2 mm. or less) in the precordial lead is often of similar significance but we believe a definitely less important sign than an absent deflection. Our studies confirm the fact that an absent initial positive deflection as the result of an anterior infarct may be followed by a small deflection after a period of a few months. Master *et al.*⁸ found that a small initial deflection was almost as frequent in posterior as in anterior wall infarcts. Analysis of our cases did not bear out this finding, though our series was considerably smaller. Our findings do confirm the statement of these authors that a small initial positive deflection is of little significance unless the second deflection of the *QRS* complex (*S* wave of new and *R* wave of old techniques) is 10 mm. or more in amplitude. The position of the precordial electrode is an important factor in the size of the initial deflection in many cases, and probably accounts for most of the variations in the size of the initial deflection seen in serial records. With this electrode placed near the sternum there is a tendency for a small or

even absent initial positive deflection in some cases which have a normal complex with the electrode placed on the apex area (Fig. 3, *A*). When a small initial positive deflection is the only abnormal electrocardiographic finding, it would seem desirable that the record be checked by another examination, with careful attention being paid to the position of the precordial electrode. This is especially true if the precordial electrode is placed on the chest routinely by a technician. As we have stated in a separate publication,⁴ we believe that the most desirable single routine position for applying the precordial electrode on the chest is at the apex area, in normal and slightly enlarged hearts, and slightly medial to the apex in patients with large hearts.

Correlation of the *T*-wave findings in Leads I and IV with the absent and small initial positive deflections in the precordial lead (IV) (Tables 1 and 2) shows a much higher per cent of abnormal *T* waves in the absent initial deflection group than in those with small initial deflections. In the group of cases with absent initial positive deflections and a definite diagnosis of old or recent myocardial infarction, the *T* waves were abnormal in 97% of the (68) cases in one or both of these leads. They were abnormal in both of these leads in 81% of the cases. In the small initial positive deflection group the *T* waves were abnormal in 59% in either lead and in only 35% of the cases in both Leads I and IV. This would seem further evidence proving the greater significance of the absent as compared to the small initial positive deflection. If the absent or small initial positive deflection is accompanied by abnormal *T* waves in any lead, especially Leads I or IV, the chances are greater that cardiac damage is present. The presence of these abnormalities even alone, however, is strong evidence of cardiac involvement.

Summary. 1. The electrocardiograms and clinical histories of 102 patients with an absent initial positive deflection in the precordial lead (*R* wave of new and *Q* wave of the old technique), and 46 patients with a small initial positive deflection (2 mm. or less) have been reviewed.

2. The most frequent cause of an absent initial positive deflection (67%) was a previous anterior myocardial infarction. In the other patients with this abnormality, organic cardiovascular disease was present in all instances, usually arteriosclerotic or luetic heart disease, with or without hypertension. Cardiac enlargement and myocardial damage from other causes may also be factors causing disappearance of this wave.

3. When the initial positive deflection is absent in the precordial lead, the *QRS* complex rarely returns to normal. An *absent* initial deflection may be followed by a *small* initial deflection in some cases of myocardial infarction and occasionally either of these signs may be the only residual electrocardiographic finding in this condition.

4. A small initial positive deflection in the precordial lead (2 mm.

or less) is a less important sign than an absent one. It is occasionally seen in normal hearts but usually is of similar significance to an absent initial positive deflection.

5. The importance of proper application of the precordial electrode is emphasized, especially in relation to the size of the initial positive deflection of the *QRS* complex.

6. A correlation between the *T*-wave findings in the precordial lead and Lead I with the absent and small initial positive deflections shows a larger per cent of abnormal *T* waves in the absent deflection group. The presence of an abnormal *T* wave in one or both of these leads with a small or absent deflection in the precordial lead makes the latter sign of greater significance. In general, *T*-wave abnormalities are less permanent than the *QRS* abnormalities in the precordial lead.

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ALLERGY AS A FACTOR IN THE DEVELOPMENT OF REACTIONS TO ANTI-RABIC TREATMENT.

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RABIES as a disease entity is one of the oldest known. Records of its existence date from the time of Aristotle. Celsus, in the first century A. D., was the first to give a detailed description of human rabies, and to state that the disease was the result of a bite by a rabid animal. Centuries passed but nothing of importance was added to our knowledge of the disease until 1879 when Galatier and Pasteur proved that rabies was an infectious disease. The famous experimental work of Pasteur followed, and in 1885 the Pasteur treatment was introduced as a prophylactic measure in the treatment of rabies.

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However, between the years 1885 and 1898 doubts developed concerning the safety of this preventive measure because of the occasional occurrence of paralyses during or after the course of treatment. These paralyses were believed to be due to the street virus or the result of its modification in the course of treatment. In 1898, Tonin²⁰ opposed this view by recording a case in which paralysis developed in spite of the fact that the animal suspected of having rabies never developed the disease. He suggested therefore, that the paralysis was due to the treatment *per se*.

Incidence of Paralytic Accidents. Considering the frequency with which the Pasteur treatment is administered, the incidence of accidents resulting from such treatment is fortunately of rare occurrence. Nevertheless, the fact that they do occur and that they may be extremely severe, constitutes a serious objection to the treatment unless positively indicated. At the First Rabies Conference of The League of Nations¹⁴ a study of the accidents resulting from the Pasteur treatment (and its modifications) revealed the development of 329 accidents in 1,164,264 persons treated. Since then McKendrick^{13a,b} has reported an additional 33 cases in 170,904 persons who were treated between 1926 and 1930. From the combined reports, the incidence of paralytic accidents appears to be 1 case per 3668 treatments, (0.027%).

The North Carolina State Board of Health has distributed approximately 24,000 courses of anti-rabic treatment (Calmette modification) and has endeavored to record all severe accidents attributable to the treatment. At the present time 20 such cases have been reported. The incidence of accidents with the treatment has been 1 per 1200 (0.083%). The mortality rate of those suffering untoward reactions has been, in this State, approximately 10% as compared with a mortality rate of 16% recorded by Remlinger and others.¹⁴ In spite of the relatively small group of patients receiving treatment through the State Board of Health, these percentages are of significance in that physicians in this State, using the State-prepared vaccine, have without hesitation revealed their misfortune to the Health Laboratory. This is in contrast to some Pasteur Institutes which, for statistical or other reasons, have been reluctant to reveal their own unfortunate results.

Classification of Reactions. In administering the Pasteur treatment one should be mindful of the various types of reactions that may be encountered. For practical purposes these can be divided into 6 groups:

GROUP 1. The prompt development of a *generalized urticarial rash* which responds to the use of adrenalin, and which usually develops in those who have been sensitized by the previous injection of nervous tissue. These cases are relatively infrequent and are without mortality.

GROUP 2. *Delayed reactions of the tuberculin type* occurring at the

site of injection and characterized by local redness, induration, tenderness, and itching. They are the most common type of local reaction encountered. They occur early during the treatment, but are not of serious import.

GROUP 3. *Reaction of the type described as Group 2, but more severe*, and frequently associated with constitutional reactions consisting of headache, low-grade fever, lymph node enlargement, nausea, and general feeling of malaise. Subsequent injections are apt to cause a flare-up at the previous injection sites. It is in these patients that one should observe closely for signs of the development of paralysis, and judge their treatment accordingly. These cases are less common than those described in Group 2.

GROUP 4. *The simple peripheral neuritic form*, following a short febrile attack and commonly involving the facial nerve.

GROUP 5. *A dorso-lumbar myelitis*, usually occurring during the second or third week of treatment, and characterized by the gradual onset of fever, weakness, numbness, tingling of the lower extremities, sphincter disturbances, and terminating in paralysis of the extremities. The local reactions are of the more severe type described under Group 3. The mortality rate is low.

GROUP 6. *Paralysis of the Landry type*, which is sudden in onset and is associated with high fever, nausea, insomnia, vomiting, headache, girdle pains, retention of urine, and an ascending paralysis. About one-third of these patients die of bulbar paralysis. Local reactions are those of Group 3.

To the types of reactions mentioned above may be added the case which is reported below. A thorough review of the available literature reveals no comparable case. The majority of the accidents previously reported are typically encephalomyelitic, whereas this case manifested an encephalitis without any paralysis.

Case Report. *Duke Hosp. No. 1921. A white male of 22 bitten by a cat suspected of having rabies: anti-rabic treatment: development of encephalitis after twelfth treatment: complete recovery.* H. M. H., a 22-year-old medical student, while working with a cat, was bitten and scratched. The animal had been exposed to rabies and treatment was advised. He received his first injection of the Calmette modification of the Pasteur treatment on the sixth day following exposure. The injections were given subcutaneously, 4 injections in the back alternating with 4 in the abdomen. Following the fifth injection the axillary lymph nodes enlarged and became quite tender. Following the sixth injection, sites of previous injections became moderately red, tender, and indurated. There was a generalized pruritus, but no rash developed. These signs and symptoms were progressive and at the time of the twelfth injection the patient complained of headache, backache, restlessness, fever, loss of appetite, and nausea. He was given the twelfth treatment and instructed to remain in bed. The following day, because of an increase in the severity of the symptoms, he was admitted to the hospital. Upon admittance the patient appeared acutely ill. He was very drowsy, had great difficulty in concentrating, and answered questions slowly. He complained of a severe headache and of being nauseated. His features were expressionless. The temperature was 39.5° C., pulse 100, respirations 20.

The general physical and neurologic examinations were negative except for marked induration at the injection sites, generalized glandular enlargement, difficulty on convergence of the eyes, slight papilledema, and a slightly stiff neck. The patient's history was interesting in that his paternal grandfather had asthma, his father and brother hay fever, and his mother exhibited marked idiosyncrasies to various foodstuffs. The patient was moderately sensitive to horse serum, was subject to sinusitis, and a Brucella skin test (given 1 year earlier) gave a 4+ reaction with necrosis and sloughing of the tissues of the forearm. His habits were regular and he had previously enjoyed excellent health.

Following admission to the hospital his condition became progressively more acute. The temperature remained elevated (38.5° to 39.5° C.), the headache became more severe, and the anorexia and sense of nausea persisted. He vomited occasionally, and he developed a rather marked bradycardia (48 to 52). The lethargy increased and by the third hospital day he was quite stuporous. On lumbar puncture, the fluid was found to be under a pressure of 250 mm. of spinal fluid. Examination of the fluid revealed 164 mononuclears and 2 neutrophils per c.mm. of spinal fluid; Pandy, 1+; the colloidal mastic test gave a 3332100 curve; colloidal gold test, benzidene reaction and bacterial cultures were negative. The puncture caused a transitory improvement in his condition. A second lumbar puncture was done on the fifth hospital day and the fluid was found to be under a 270 mm. pressure, but there was no appreciable change in the character of the fluid. This procedure was again followed by improvement in his general condition. A third lumbar puncture was done 6 hours later. On the sixth hospital day he appeared markedly improved. He was alert, rational, conversational, and relatively comfortable. The pulse rate was 70 and the temperature 38° C. Rabbits and guinea pigs inoculated with the spinal fluid remained healthy. Blood and spinal fluid Wassermanns were negative.

In spite of the marked improvement in his general condition he complained of extremely severe generalized headaches and some impairment of taste. Improvement was steady and the patient was discharged on the fourteenth hospital day.

The patient's family history, and the manner in which he reacted to the vaccine, suggested strongly that the local reactions and early manifestations of generalized lymph node enlargement might be viewed as an allergic response to the protein contained in the nervous tissue of the vaccine, and that the clinical picture of encephalitis which followed might likewise be an allergic response to the protein of the inocula.

Etiology. Since the case reported by Tonin,²⁰ the nature of paralytic accidents has been a constant and interesting source of controversy. Koch¹¹ believed that the paralyzes were due to canine rabies. Babes² attributed them to a rabies toxin, and Marinesco¹⁵ to the deleterious action of normal nerve substance. França,⁸ Fielder,⁷ Busson,⁵ von Stockum,²¹ and others were of the opinion that they resulted from the action of the fixed virus of the inocula. At the Rabies Conference,¹⁴ Calmette supported the theory that paralyzes were due to a neurotropic virus contained in the cord of the rabbit and inoculated with the vaccine. Bassoe and Grinker,³ because of a similarity in the pathologic features of fatal neuropa-

lytic accidents associated with the administration of the Pasteur treatment, and those of non-vaccinal encephalomyelitis found in variola, measles, and other virus diseases, believed they were "dealing with an inflammatory disease caused by an attenuated virus." For similar reasons Marsden and Hurst¹⁶ were of the opinion that paralyzes were caused by a "single clinical and pathologic entity," namely, a virus. Remlinger¹⁴ and Stuart and Krikorian¹⁹ subscribed to a "cytotoxic" theory and believed that the reactions resulted from "the introduction of an excessive amount of foreign nerve protein" during the course of treatment, and that the nature of this protein must have been changed by its treatment with carbolic acid so as to render it toxic. Stimson¹⁸ and McKendrick (Rabies Conference)¹⁴ believed that the accidents were the result of anaphylactic reactions to the inocula. Prausnitz¹² adhered to the idea that the paralyzes were due to the injection of heterogenous nerve substance in specially predisposed individuals, while Cornwall⁶ suggested that they were allergic reactions resulting from the injection of foreign nerve protein.

Schwentker and Rivers¹⁷ have found that brain tissue under proper conditions functions as a "complete antigen and is capable of exciting in rabbits the development of complement-fixing antibodies which are organ, rather than species specific." This discovery, they believe, "opens again, for the brain at least, the question of the etiologic rôle of organ-specific antibodies in certain degenerative diseases . . . and strengthens materially the hypothesis that the encephalomyelitis which follows anti-rabies vaccination is in some manner associated with the development of specific antibodies for brain."

The case just cited presents several features which are worthy of emphasis. A previously healthy person of regular habits suffered reaction to the Pasteur treatment; there was a marked individual and family history of allergic disease; the local reactions were of the severe delayed tuberculin-like type and were associated with a constitutional reaction; and superimposed upon this there developed the clinical picture of encephalitis. These features were sufficient to suggest that the reaction was in the nature of an allergic response to the protein of the inocula and suggested the following investigations.

Investigation. A survey was made of 16 persons known to have had severe accidents as the result of treatment. Each individual was interviewed personally and questioned with regard to the following points: (a) the presence of an individual or family history of allergic disease; (b) the type of local reaction and its relation to the beginning of the treatment; (c) the type of accident, its symptomatology and relation to the beginning of treatment; (d) the total number of injections given; and (e) the degree of recovery following the accident. In addition, such factors as age, race, occupation,

site of exposure, type of local treatment, and the presence of the so-called "predisposing factors," such as physical or mental strain, nervous or mental disease, living conditions, use of alcohol or drugs, and a history of syphilis were considered.

As a result of this survey it was found that 80% of these patients gave a personal history of asthma, hay fever, urticaria, or marked food idiosyncrasies; that there was a positive family history of allergic disease in 50% of the cases; and that there was either an individual history, family history, or both in 87.5% of the patients interviewed. The local reactions in 80% of the cases were of the severe delayed type described under Group 3, and the remaining 20% were of the delayed type of Group 2. The local reactions began in the majority of the cases about the third or fourth day after treatment had begun, became progressively more severe, and persisted throughout the time that the vaccine was administered. Evidence of neuro-dysfunction began on an average of 15 days after treatment was started. Recovery had occurred, or was occurring, in all but one case (Table 1, Case 4). Of those from whom no allergic history was obtained, one (Table 1, Case 6) drank alcohol excessively throughout the course of treatment, and the other (Table 1, Case 11) was a child of unknown paternity and consequently no reliable family history could be obtained. The results are summarized in Table 1.

TABLE 2.—ALLERGY INCIDENCE IN THOSE RECEIVING RABIES PROPHYLAXIS.

	Personal history of allergic disease, per cent.	Family history of allergic disease, per cent.	Personal and (or) family history of allergic disease, per cent.	No history of allergic disease, per cent.
Sixteen persons suffering treatment accidents	80	50	87.5	12.5
Forty-five persons not suffering treatment accidents	30	20	33.3	66.6

Following the same procedure as was used in taking histories from those who suffered treatment accidents, a control series of 45 persons who had taken the Pasteur treatment without complications were interviewed. The cases were not selected. From this study there developed 4 interesting facts: (1) a positive individual allergic history was obtained in 30%; (2) there was a positive family allergic history in 20%; (3) there was either an individual history, family history, or both in 33% of those interviewed; and (4) there was a rather marked correlation between the severity of the local reactions and the presence of a positive history of allergic diseases.

In comparing these percentages of both groups, it will be seen that in those suffering unfavorable reactions to treatment a history of allergic disease, either personal or familial, or both, was obtained in 87.5% of the cases. In the control series, a similar history was obtained in only 33.3% of those questioned. From this it would

appear that the much higher incidence of allergic disease in the group suffering treatment accidents, in contrast to the group taking the treatment without the development of accidents, was more than a matter of chance, and that allergy played a rôle in the development of treatment accidents (Table 2).

Methods and Results of Desensitization. The occurrence of neuro-paralytic accidents is not confined to the use of anti-rabies vaccine, for they are known to occur following the use of typhoid vaccine and various types of serotherapy. Kennedy,¹⁰ Young,²² Gayle,⁹ and Allen¹ have reported such cases and the clinical manifestations are similar to those of the accidents which occasionally attend the administration of the Pasteur treatment.

These, and other reactions to vaccines and serums, are generally thought to be due to foreign protein, and, especially in the case of serum therapy, several well recognized procedures are followed in an effort to prevent their development. First, patients are skin-tested, and if found to be sensitive are desensitized. Second, if during the course of treatment they acquire a sensitivity to the inocula, treatment is stopped and a process of desensitization is begun. Following these simple procedures the inocula may be given with relative impunity and the majority of reactions to treatment avoided. Recently we have given the Pasteur treatment to several persons and have had the opportunity of observing and applying these procedures to those who were or became sensitized to the inocula. The procedure was as follows:

1. Patients to whom the treatment was to be given were skin tested with a 1 to 10 dilution of the No. 1 cord. If a typical allergic wheal developed rapid desensitization was begun, the injections being given every 15 minutes, starting with 0.2 cc. of 1 to 10,000 dilution of No. 1 cord, and continued until the undiluted vaccine was given without reaction.

2. Patients who became sensitive during the course of treatment were given a more gradual method of desensitization, the initial desensitizing dose being determined by that dilution which was tolerated without a local reaction or inciting a reaction at a previous injection site. Daily injections, beginning with 0.5 cc. of the diluted vaccine, were given until the undiluted vaccine was tolerated.

Case 1.—Mr. W. T., university student, aged 25, was bitten by a dog whose behavior was suggestive of rabies. Laboratory examination of the animal's brain was unsatisfactory. The patient's history was of interest in that several members of his family were "very nervous and highly strung," and that there was an individual and family history of allergic disease. His habits were regular and he denied venereal disease. He had never before taken the Pasteur treatment. Treatment was started on August 6th, 1935. Approximately 40 minutes after the first injection the patient returned complaining of "itching rash" over his face and body. Examination revealed many urticarial wheals varying from 2 to 4 cm. in diameter. The injection site was red and indurated and measured 8 cm. in diameter. Adrenalin,

TABLE 1.—SUMMARY OF 16 PATIENTS SUFFERING UNFAVORABLE REACTIONS TO THE PASTEUR TREATMENT.

Patient.	Sex.	Age.	Race.	Animal.	Number of days between exposure and treatment.	Interval between beginning of treatment and development of			Number of injections given.	Type of paralysis.	Result.	Allergic history.		Remarks.	
						Local reaction.		Paralysis.				Individual.	Family.		
						No. days.	Type.								No. days.
1 H. B.	M.	25	W	Rabid cow	3	4	Delayed severe	19	18	Transverse myelitis	Recovery	Pos.	Pos.	Her only allergic manifestation is a violent reaction to horse serum. This was the 2d course of treatment. First was 2 yrs. before.	
2 N. L.	F.	22	W	Rabid cat	4	4	Delayed severe	12	14	Transverse myelitis	Recovery	Pos.	Pos.		
3 V. E.	F.	12	W	Rabid dog	7	6	Delayed severe	13	11	Transverse myelitis	Recovering	Pos.	Pos.		
4 G. W.	M.	48	W	No exam. dog	1	About 6	Not known to informant	11	9	Ascending paralysis of the Landry type	Death on 15th day	Pos.	Pos.		
5 R. F.	F.	24	W	Rabid dog	2	3	Delayed severe	13	16	Loss of sphincter control; weakness of extremities (marked)	Recovering	Pos.	Neg.	Used alcohol daily and excessively throughout treatment.	
6 R. D.	M.	35	W	Rabid dog	4	2	Delayed severe	12	8	Transverse myelitis	Slight residual weakness	Neg.	Neg.		
7 E. M.	M.	35	W	Rabid hog	1	About 3	Delayed slight	25	21	Transverse myelitis; unilateral paralysis of Cr. VII	Slight residual weakness	Pos.	Neg.		
8 C. I.	M.	55	W	No. exam. dog	10	5	Delayed severe	19	9	Transverse myelitis	Slight residual weakness	Pos.	Neg.		
9 B. S.	M.	3	W	Rabid cat	4	2	Delayed severe	21	21	Paralysis laryngeal branches of Cr. X	Recovery	Neg.	Pos.	Father unknown to patient or mother.	
10 H. H.	M.	22	W	Doubtful cat	6	5	Delayed severe	13	12	Encephalitis	Recovery	Pos.	Pos.		
11 J. G.	M.	17	C	Rabid dog	4	?	Delayed slight	28	21	Transverse myelitis	Recovering	Neg.	Neg.		
12 R. M.	M.	48	W	Rabid dog	1	3	Delayed severe	14	14	Transverse myelitis	Slight residual weakness	Pos.	Neg.		
13 J. B.	M.	26	W	Rabid dog	0	1	Delayed moderate	14	14	Transverse myelitis	Slight residual weakness	Pos.	Neg.	Both parents died during patient's childhood, hence no knowledge of family allergic disease. Drank upon occasions during course of treatment.	
14 J. L.	M.	40	W	Rabid dog	5	?	Delayed severe	15	15	Transverse myelitis	Slight residual weakness	Pos.	Neg.?		
15 C. S.	M.	32	W	Rabid dog	1	3	Delayed severe	24	21	Facial	Recovery	Pos.	Pos.		
16 F. B.	M.	25	W	Rabid dog	3	5	Delayed severe	12	15	Transverse myelitis	Slight residual weakness	Pos.	Pos.		
Ave.	M 8:1	29.3	..	80% known rabid	3.5	3.7	Delayed severe	16.5	14.7					Pos. family or individual hist., 87.5%	
										Pos. individual allergic hist., 80%					Pos. family allergic hist., 50%

Pos. family allergic hist., 50%

Pos. individual allergic hist., 80%

Pos. family or individual hist., 87.5%

0.5 cc., was injected with prompt disappearance of the wheals. On the following day desensitization was begun. Injections were given every 15 minutes starting with 0.2 cc. of a 1 to 10,000 dilution of anti-rabic vaccine and ending with 0.5 cc. of the undiluted vaccine. On August 8, 9, and 10 the procedure was repeated, beginning with dilutions of 1 to 1000, 1 to 100, and 1 to 10 respectively. At no time was there a recurrence of the original complaints. He remained desensitized and the subsequent course of treatment was uneventful.

CASE 2.—Miss F. P., university student, aged 21, was bitten by a dog and insisted upon taking treatment. No examination of the animal was made. Treatment was begun in April, 1936. Her history was interesting in that she had been vaccinated against poliomyelitis (Kolmer method) in September, 1935. A skin test with 0.2 cc. of a 1 to 10 dilution of the anti-rabic vaccine resulted in the prompt development of a large erythematous wheal. A process of desensitization was used similar to Case 1. The subsequent course of treatment was wholly without discomfort or reaction and at no time did she regain her sensitivity.

CASE 3.—Mrs. M., housewife, aged 34 was bitten by a dog proved by the State Health Laboratory to have been rabid. She was subject to annual attacks of hay fever. Pasteur treatment was advised. A skin test with 0.2 cc. of 1 to 10 dilution of the vaccine was negative, and the treatment was started. All injections were given in the back. After the third injection there developed a tender erythematous and indurated area at the injection site. Subsequently, local reactions rapidly became more severe, and each injection gave rise to a reaction at the previous injection site. At the time of the sixth injection these areas measured 10 to 12 cm. in diameter, were very firm, had a well demarcated margin, and were exquisitely tender. The treatment was stopped and desensitization begun, using the following plan:

- 1st day, 0.5 cc. 1:100 dilution of the vaccine.
- 2d day, 1.0 cc. 1:100 dilution of the vaccine.
- 3d day, 0.5 cc. 1:10 dilution of the vaccine
- 4th day, 1.0 cc. 1:10 dilution of the vaccine.
- 5th day, 0.5 cc. undiluted vaccine.
- 6th day, 1.0 cc. undiluted vaccine.

Under this plan the local reactions completely disappeared, and the regular treatments were resumed. After 2 injections, however, she regained to a slight degree her sensitivity, and the procedure outlined above was repeated starting with 0.5 cc. of a 1 to 10 dilution. The remaining eleven injections were given without any local reaction or discomfort.

Discussion. Burky and Henton⁴ have found that repeated injections of lens extract plus staphylococcus toxin gave rise to a skin sensitivity to lens extract, and that if the lens of a sensitized animal was injured by needling, there developed an intra-ocular inflammation that clinically and histologically resembled endophthalmitis phaco-anaphylactica. This inflammation was believed to be due to the absorption of lens protein by the hypersensitive subject. A method of desensitization was devised (using lens extract and staphylococcus toxin) and successfully applied in causing a remission of the signs and symptoms of experimental and clinical endophthalmitis phaco-anaphylactica. It was noticed by these observers that as their subjects lost their skin sensitivity there was a coincidental

improvement in the ocular signs which, they suggested, might be due to a diminished ocular sensitivity.

Schwentker and Rivers¹⁷ have demonstrated that nervous tissue is capable of exciting the development of organ-specific antibodies and that this tissue became a more effective antigen when it was altered by the addition of pig serum, treatment with vaccine virus, and especially by autolysis. They also showed that, as the result of the injection of nervous tissue into rabbits, the number of paralyses that developed paralleled the antigenic power of the emulsion used. They concluded that "these observations cannot be considered evidence that the paralyses are directly related to the antigenicity of the brain tissue emulsion because, as Hurst has pointed out, . . . they might have been induced by some toxic substance in the autolyzed or diseased brain."

In many respects the experiments of Schwentker and Rivers¹⁷ are analogous to those of Burky and Henton,⁴ namely, that an organ-specific substance plus a toxic substance occasioned the development of a sensitivity to the specific substance.

The analogy just made may be carried a step further and applied to an understanding of the reactions that occasionally attend the administration of the anti-rabic vaccine. The nervous tissue that is injected has been altered by infection with a fixed rabies virus and by desiccation. The severe local reactions preceding the onset of the symptoms of central nervous system involvement are a rough index of the degree of acquired sensitivity to the inocula. It is possible to desensitize those who are, or who become sensitive to the inocula and thus cause a remission of the signs of cutaneous hypersensitiveness. It is possible that with the loss of skin sensitivity there may also be a loss, or diminution, of a central nervous system sensitivity which would prevent or arrest the development of a reaction to the treatment.

The exceedingly high incidence of allergic disease among those suffering reactions to treatment would warrant one's questioning each candidate for the treatment concerning a personal or family history of allergy, not alone because accidents are more frequent among these individuals, but because of the severity of the local reactions they are apt to suffer. It seems advisable, therefore, that those who show or develop a marked sensitivity to the inocula should be given the benefits of desensitization.

Summary. The number of neuro-paralytic accidents among those taking the Pasteur anti-rabic treatment has been reported by McKendrick^{13a,b} as approximating 0.027%, whereas the North Carolina State Board of Health, in its more limited survey, reports an incidence of 0.083%. In North Carolina the mortality rate of those suffering paralytic accidents was 10% as compared to 16% recorded by Remlinger.¹⁴

The various types of reactions to the Pasteur treatment may be divided into 6 groups. To these is added the report of a patient who developed encephalitis without paralysis during the Pasteur treatment and which was believed to be due to an allergic response to the inocula.

As the result of an investigation of 16 persons who had suffered reactions to the Pasteur treatment it was found that there was an exceedingly high incidence of allergic disease (87.5%) as compared with a control group (33.3%) in which no neuro-paralytic accidents occurred. In the control group, the allergic individuals suffered much more severe local reactions than the non-allergic individuals.

The various theories concerning the etiology of the paralytic accidents are reviewed, showing the controversial nature of this subject.

This study suggests that a careful investigation of a patient's allergic background and a determination of his sensitivity to the anti-rabic vaccine are valuable measures in determining those individuals who may suffer reactions to the treatment.

A method of desensitization was successfully employed in 3 cases that had, or developed, a marked sensitivity to the anti-rabic vaccine.

A hypothetical analogy is drawn between endophthalmitis phacoanaphylactica, and the unfavorable reactions to the Pasteur treatment. It is suggested that as the result of desensitization, evidenced by the loss of skin sensitivity, there may likewise occur a loss of central nervous system sensitivity. Such a loss of sensitivity would prevent or arrest the development of neuro-paralytic accidents associated with the Pasteur treatment.

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STUDIES ON CALCIUM CREOSOTATE.

IV. OBSERVATIONS ON ITS USE IN PULMONARY TUBERCULOSIS.*

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PREVIOUS experimental work^{6a, b} has shown that calcium creosotate compared closely with the creosote from which it was prepared although slight chemical differences^{6c} existed between the two drugs. Creosote and its preparations receive widespread application in the treatment of pulmonary disorders despite the fact that a satisfactory explanation of their action has not been advanced. Statements are to be found that under certain conditions⁵ expectoration is lessened; while under certain other conditions, the secretion of mucus is believed¹² to be increased during their administration. At the present time, there is a discrepancy of opinion as to the value of creosote and its preparations in the treatment of pulmonary diseases. Recently, Brown² has stated that calcium creosotate is of value in chronic inflammatory conditions and that it is especially useful when the sputum is abundant as in lung abscess, bronchiectasis, and suppurative pneumonitis. On the other hand, the Council on Pharmacy and Chemistry of the American Medical Association stated¹ that all creosote preparations were to be omitted from New and Non-official Remedies because they believed their use was based purely on empiricism.

The primary purpose of the present investigation was to determine whether or not any modification of 24-hour sputum specimens could be demonstrated during a period of calcium creosotate administration. Patients with pulmonary tuberculosis have been selected because it has been possible to collect reasonably constant amounts of sputum from these individuals, whereas in most bronchial diseases the daily variation in sputum volume is so great that it is impossible to obtain reliable control data. In the present experiments, the volatile phenol content of 24-hour sputum specimens has been investigated both before and during periods of drug administration to determine the presence or absence of the drug in contact with the bronchial mucosa. Estimations of the volatile phenols excreted in urine of patients receiving calcium creosotate have been made as an indication of its absorption. Attempts also have been made to detect phenolic substances in the expired air of experimental animals after calcium creosotate had been administered.

Method. The sputum data in this communication have been obtained from 3 series of hospitalized patients.† Each series as nearly as possible

* The expense of this investigation was defrayed, in large part, by a grant from The Maltbie Chemical Company, Newark, New Jersey.

† All cases referred to in this communication were patients at Eagleville Sanatorium, Eagleville, Pa.

was made up of individuals showing similar degrees of lung change. The procedure has been to compare data secured during satisfactory normal periods of observation with that obtained during drug administration. Approximately one-half the patients of a given series were continued as controls.

Twenty-four-hour sputum specimens were collected in bottles and their volumes estimated therein by comparison against a measured quantity of water. Prior to the phenol determination all specimens were autoclaved at 20 pounds pressure for 40 minutes. Control experiments in which known amounts of creosote were added to 24-hour specimens just before autoclaving demonstrated that volatile phenolic material was not lost in this process. Each autoclaved specimen was treated with 15 to 20 cc. of concentrated phosphoric acid (85%) and steam distilled until 250 to 300 cc. of distillate had been collected. Due to the small amounts of volatile phenols present in the 24-hour specimens it was necessary to extract the distillates, previously acidified by the addition of a few drops of HCl, with ethyl ether. Three extractions of each distillate with 50-cc. portions of ether invariably resulted in a phenol free aqueous layer. The ether was then evaporated, the residue taken up with 60 cc. of distilled water and this treated with 10 cc. of para-diazo-nitraniline. After 3 minutes it was made alkaline by adding 5 cc. of 10% NaOH solution and compared in a colorimeter against a known creosote solution treated in the same manner. Concentrations of 1 to 2 mg. of creosote per 100 cc. when treated with diazotized nitraniline reagent and made alkaline will give a red violet color. Solutions containing 0.2 to 0.5 mg. creosote per 100 cc. will give an orange yellow color. When the diazotized nitraniline reagent itself is made alkaline a green yellow color is produced. Most sputum specimen distillates gave an orange yellow color the intensity of which was seemingly dependent upon the amount and character of the sample distilled. This color has been attributed to volatile phenols but it must be said that no attempt was made to determine the nature of this material. Phenol concentrations of less than 0.2 mg. have been designated in the tables as traces.

Determinations of total volatile phenols eliminated in urine during 24 hours by 4 of the patients receiving four 0.25 gm. calcium creosotate tablets 3 times a day were made in the manner previously described.^{6b}

Results and Discussion. Results of the observations made on the first series of patients examined have been placed in Table 1. Each sputum volume recorded in this table is an average of 30 determinations. The sputum volatile phenol values in this and all succeeding tables represent the highest and lowest obtained either before or during a period of drug administration. The total period of observation for this series extended over 3 months; the actual time of drug administration was 1 month. In this and all other series the patients were given an initial dose of one 0.26-gm. calcium creosotate tablet 3 times a day. The amount of the drug given was gradually increased if the patients were not nauseated by this initial dose. The drug was always administered after meals with a copious amount of water. In this series, it was impossible to give more than 2 tablets 3 times a day. After the drug had been given for a period of 1 month it became necessary to discontinue this series because practically every individual of this group was nauseated. It is to be noted that the sputum phenols of the patients receiving the drug did not increase during this period. In computing the average

normal sputum volumes it was observed that most of the specimens remained remarkably constant from day to day.

The grand average of the sputum volumes of those patients receiving the drug shows a loss of 1.7 cc., whereas that of the control patients shows a loss of 2.09 cc. during the same period. In other words, the sputum volumes of both groups remained remarkably constant. The character of the 24-hour sputum specimens was described each day but insufficient change was noted in any case to warrant tabulation of the data.

TABLE 1.—VOLATILE PHENOLS AND VOLUME OF SPUTUM. FIRST SERIES.

Receiving drug.	24-hour sputum volumes— average of 30 observations.		24-hour sputum volatile phenols.	
	Before drug administration, cc.	During drug administration, cc.	Before drug administration, mg.	During drug administration, mg.
V. G.	3.0	4.2	traces	traces
J. C.	4.1	4.5	traces	traces
L. M.	5.1	6.9	tr.-0.2	traces
F. H.	12.8	14.3	tr.-0.2	tr.-0.2
S. B.	6.0	5.2	traces	traces
T. K.	12.8	10.0	tr.-0.2	tr.-0.2
A. G.	4.6	2.8	traces	traces
X. K.	6.0	4.0	traces	traces
C. M.	5.0	5.3	traces	traces
Z. M.	14.5	10.4	tr.-0.2	tr.-0.2
L. ST.	2.4	2.1	traces	traces
W. K.	75.0	69.0	0.5-0.6	0.5-0.7
V. M.	121.0	110.0	0.6-0.8	0.6-0.8
J. L.	28.2	28.0	tr.-0.4	0.2-0.4
Grand average . .	21.4	19.7		
Controls.				
A. B.	3.3	4.7	traces	traces
A. L.	48.5	25.5	0.3-0.5	0.4-0.5
L. R.	25.3	26.0	tr.-0.4	tr.-0.4
T. B.	52.4	46.2	0.2-0.3	tr.-0.3
H. F.	37.5	36.0	0.2-0.3	tr.-0.3
J. M.	3.7	3.2	traces	traces
L. Sp.	31.0	39.7	tr.-0.3	tr.-0.2
P. S.	18.6	20.6	tr.-0.3	tr.-0.3
H. G.	3.8	6.0	traces	traces
E. R.	10.7	6.0	traces	traces
Grand average . .	23.48	21.39		

The control observations of the second series extended over 3 months. One-half of this group then received the drug for 5 consecutive months. Each sputum volume recorded in Table 2 for patients of this series is the average of 50 determinations. No significant variations are to be noted in the group of patients receiving the drug as compared with the control group. This applies to individual patients as well as to the grand averages. It is to be noted also that in this group the sputum volatile phenols did not increase during the period of drug administration. These data should be accepted as conclusive because the majority of the patients

receiving the drug were given four 0.26-gm. tablets 3 times a day throughout the 5 consecutive months. After a control period of 7 days the patients of this series receiving calcium creosotate were given 0.3-gm. terpin hydrate 3 times a day for 7 days. It is to be noted in Table 3 that no significant change in volume was observed during this period.

TABLE 2.—VOLATILE PHENOLS AND VOLUME OF SPUTUM. SECOND SERIES.

Receiving drug.	24-hour sputum volumes— average of 50 observations.		24-hour sputum volatile phenols.	
	Before drug administration, cc.	During drug administration, cc.	Before drug administration, mg.	During drug administration, mg.
F. H.	14.0	13.0	tr.-0.35	0.2-0.3
M. T.	20.5	18.2	0.25-0.4	tr.-0.4
L. S.	2.3	5.8	traces	traces
M. M.	4.3	5.9	traces	traces
W. M.	18.3	21.4	tr.-0.2	tr.-0.2
A. D.	23.7	24.1	tr.-0.25	tr.-0.2
R. T.	32.4	26.3	0.25-0.35	tr.-0.03
C. A.	41.7	40.4	0.4-0.5	0.3-0.5
L. M.	16.2	19.1	0.2-0.3	tr.-0.3
J. C.	5.4	6.0	traces	traces
N. H.	37.4	31.1	0.25-0.35	0.2-0.3
M. S.	16.1	15.7	0.2-0.3	tr.-0.3
D. B.	8.3	13.4	tr.-0.2	0.2-0.25
L. Si.	24.1	28.0	0.2-0.3	0.2-0.4
L. Sp.	81.8	72.6	tr.-0.3	tr.-0.2
Grand average . .	22.8	22.7		
Controls.				
V. G.	4.6	5.1	traces	traces
T. B.	27.5	29.9	0.2-0.25	0.2-0.25
J. L.	28.0	29.9	0.25-0.35	0.2-0.3
L. M.	10.7	10.4	0.2-0.25	tr.-0.2
E. M.	50.1	41.0	0.3-0.45	0.2-0.4
F. M.	8.0	11.8	traces	traces
R. R.	7.4	9.0	0.2-0.3	tr.-0.3
I. M.	30.4	24.0	tr.-0.3	0.2-0.3
M. L.	3.0	4.0	traces	traces
A. G.	2.4	2.6	traces	traces
J. Cl.	4.7	3.6	traces	traces
H. F.	50.4	44.0	0.2-0.3	0.2-0.4
G. M.	5.0	6.1	traces	traces
A. B.	5.3	6.6	traces	traces
P. S.	24.1	25.8	0.2-0.3	tr.-0.3
J. W.	8.2	13.7	0.2-0.3	tr.-0.3
D. S.	8.3	7.5	traces	traces
Grand average . .	16.36	16.17		

Data also were obtained from 18 patients who were soon to be discharged. It was believed that the individuals of this series would show less tendency to become nauseated than the members of the previous groups. The opposite proved to be true, so that at the end of 4 weeks this series had to be discontinued though the amount of drug administered was only one or two 0.26-gm. tablets 3 times a day. As in the previous groups investigated, the variations

in sputum volumes shown by patients receiving the drug were no greater than the variations shown by the control patients. The sputum phenols also were not increased during the period of drug administration. It is possible that statements in the literature concerning the sputum volume changes after creosote may be the result of isolated observations on individuals who might have shown the same changes without the drug. In the present experiments, the sputum volumes of certain of the patients increased considerably while in others it decreased during medication. However, it must be emphasized that the same degree of change was noted in the control patients.

TABLE 3.—VOLUME OF SPUTUM. THIRD SERIES.

Patients.	24-hour sputum volumes—average of 7 observations.	
	Before terpin hydrate administration, cc.	During terpin hydrate administration, cc.
F. H.	15.4	23.0
M. T.	11.1	9.1
L. S.	2.1	2.4
W. M.	11.5	9.0
A. D.	14.6	15.3
R. T.	21.5	17.0
C. A.	23.6	23.1
M. M.	4.6	2.8
L. M.	13.8	7.6
N. H.	36.1	37.0
M. S.	11.1	10.2
Average	15.0	14.2

Groner⁸ states that the appetites of tuberculous patients are increased by guaiacol and creosote. He believes this is to be explained by an intestinal antiseptic and gastrosecretory stimulant action. In the present investigation no evidence of lessened cough, greater ease of expectoration, or increased appetite was obtained for those individuals receiving calcium creosotate.

TABLE 4.—VOLATILE PHENOLS IN URINE.

Patients.	Twenty-four hour specimen—average of 8 determinations.	
	Before calcium creosotate administration, mg.	During calcium creosotate administration, mg.
J. C.	35	985
A. D.	20	770
N. H.	25	850
R. T.	18	980

A number of individuals have reported that creosote is valueless in tuberculosis but is of value in certain other conditions. Dube, for example,⁴ believes creosote of no value in tuberculosis, except

where there are associated coccal infections. In pneumonia, he states the temperature is lowered, the patient breathes more easily, expectoration is less viscous and more easily expelled. McKinley¹⁰ used creosote enemata in lobar pneumonia and states that temperatures were lowered and the crisis hastened. He believes the action of creosote in purely pneumococcic conditions to be almost specific. Merrilles¹¹ states that creosote is of no value in other than coccal infections. He also believes that in pneumonia and meningitis creosote is more or less specific.

Bufalini³ reported that phenols were not excreted in the expired air of rabbits after subcutaneous or oral administration of creosote or guaiacol. In his experiments, the expired air was collected in NaHCO_3 solution and tested for phenols by adding Lugol's solution and estimating the excess iodine.

Failure in the present experiments to find evidence of excretion of phenols in the sputum specimens of those individuals receiving calcium creosotate suggested the necessity of investigating expired air of animals given the drug. Each of 6 rabbits was given by stomach tube 0.5 gm. of water soluble calcium creosotate phenols, muzzled, and the expired air collected in a 5% NaOH solution for periods of 8 hours in some cases, to 18 hours in others. At the end of these intervals the absorption liquid was neutralized with HCl , para-nitraniline reagent added and made alkaline with NaOH solution. A very slight darkening sometimes took place when the absorption fluid was treated with para-nitraniline reagent, but absorption fluid from control rabbits also exhibited the same phenomenon. Therefore in these experiments no evidence was obtained for the presence of phenolic material in the expired air of animals given calcium creosotate.

Gordonoff⁷ has reported experimental demonstrations of an "expectorant" effect after guaiacol. He also has reported finding concentrations of 1 to 5000 to 1 to 10,000 of the drug in extirpated lungs of rabbits previously given from 1 to 1.5 gm. of guaiacol. From his results he concluded that guaiacol exerted an expectorant effect by virtue of a secretory and motor action. Gordonoff failed to report the phenol concentrations in other organs of the body. On the other hand, Hofbauer⁹ has reported that when guaiacol is injected hypodermically, the major part is contained in the blood, liver and spleen, much less in the lungs and kidneys.

In our experiments, failure to find evidence of excretion of calcium creosotate phenols in 24-hour sputum specimens during drug administration coupled with the failure to detect phenols in the expired air of animals, leads one to doubt the presence of appreciable amounts of calcium creosotate along the bronchial mucosa. Walters¹³ has stated that creosote acts mainly (or entirely) on associated infections in tuberculosis. From the results of the present experiments this is difficult to visualize.

The data obtained for the volatile phenol content of 24-hour urine specimens from 4 of the patients receiving four 0.26-gm. tablets of calcium creosotate 3 times a day have been recorded in Table 4. The figures represent the average values obtained during 8 different days. These values appear to be rather high if one considers only certain phases of previous chemical investigations^{6c} on calcium creosotate. In these experiments,^{6c} it was shown that approximately one-fourth of calcium creosotate powder was made up of water soluble phenols. On this basis, these patients received in the calcium creosotate tablets approximately 750 mg. of water soluble phenols daily. As shown in Table 4, these patients excreted phenols in excess of this amount. Numerous investigators have shown that only a fractional part of orally administered phenols are excreted in urine. In the work cited above,^{6c} in addition to demonstrating that one-fourth of the calcium creosotate powder was made up of water soluble phenolic material, it also was shown that 56% of the drug was made up of organic material. No attempt was made to identify the 30% of water insoluble organic matter. The present high urine phenol values after calcium creosotate tablets suggest the possibility that the water insoluble organic material may be phenolic in nature, soluble in the gastro-intestinal secretions and hence absorbed. Another explanation of the high values may be that since the drug was administered 3 times a day and the 24-hour urine specimens collected only at irregular intervals there may have been overlapping of doses.

The nature of calcium creosotate phenols excreted in human urine was not investigated in the present experiments. In other experiments using rabbits^{6d} it was shown that practically all orally administered calcium creosotate was excreted in rabbit urine in conjugated form.

Summary. 1. Administration of calcium creosotate to patients with pulmonary tuberculosis failed to modify the volume or character of their 24-hour sputum specimens.

2. A number of individuals in the groups investigated tolerated large doses (3.1 gm. daily) of calcium creosotate for periods of several months. On the other hand, some were severely nauseated in short intervals by 0.75 gm. daily.

3. Evidence is presented to show that none of orally administered calcium creosotate was excreted in sputum specimens of the patients investigated.

4. No evidence was obtained to indicate that the patients receiving calcium creosotate expectorated more easily, that their cough was lessened or appetites increased.

5. The detection of large amounts of volatile phenols in urine after administration of calcium creosote is evidence of its absorption in man.

6. Volatile phenols could not be detected in expired air of rabbits after calcium creosotate had been administered.

We wish to express our thanks to Dr. Louis Cohen whose efforts have made possible the coöperation between Eagleville Sanatorium and this department. Grateful acknowledgment is also made to Dr. A. E. Livingston for the many helpful suggestions and encouragement given during the course of these experiments.

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THE EFFECT ON THE DEVELOPING RED BLOOD CELLS IN THE FETUS, OF ADMINISTERING HUMAN AND HOG GASTRIC JUICE TO THE ADULT RAT DURING PREGNANCY.

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THE hematopoietic factors which control the progressive reduction in the size and volume of the erythrocytes during the development of the fetus and maintain their normal values during adult life are not entirely understood. It is known that antianemic substances occur in adult liver and in gastric juice as well. Castle and his associates⁴ expressed the opinion that there is an extrinsic factor in food, which coupled with an intrinsic factor in gastric juice forms the antianemic principle. Morris and his co-workers¹⁶ and Green-

spon⁹ attributed the hematopoietic potencies to gastric juice alone. Other workers^{5,24,29} have demonstrated antianemic substances in desiccated whole stomach. Meulengracht¹⁴ claimed that desiccated gastric mucosa removed from regions of the pylorus and from areas associated with Brunner's glands contains a potent stimulus for red blood cell stimulation. After total gastrectomy in the hog, the amount of antianemic principle stored in the liver was considerably less than in the normal animal.^{1,8} Macrocytic anemia developed in a hog 3 years after total gastrectomy,¹ but Mann and Graham¹³ found no changes in the blood picture of a dog 7 years after removal of the stomach. Thus the stomach is not the only source for antianemic principle in all species. Richter, Ivy and Meyer¹⁹ found that desiccated whole stomach of the dog does not contain as much of the antianemic principle as does desiccated stomach of the hog; the principle is nevertheless present in dog's liver. Reimann and his associates¹⁸ failed to demonstrate any hematopoietic factor in gastric juice obtained from a horse, while Richter, Meyer and Ivy²⁰ showed that it is present in the liver of the horse. Wintrobe, Kinsey, Blount and Trager³² could not demonstrate an antianemic factor in fetal liver; but Goldhamer, Isaacs and Sturgis⁶ stated that it is present in human fetal liver 2 months before birth. Goldhamer and others concluded that, since not all livers contain the active principle, its presence in the liver indicates that it is a storage product.

Bio-assay of the antianemic principle has not given consistent results. Pigeons,²⁶ guinea-pigs¹¹ and rats²⁵ have been employed but results have been contradictory. Singer²³ claimed that rats kept on a standard diet show a constant elevation of the percentage of reticulocytes in response to normal gastric juice administered parenterally. Gastric juice of patients suffering from pernicious anemia, or gastric juice heated to temperatures of 100° C. failed to elicit comparable reticulocyte responses. Gastric juice which had been ultrafiltrated and which was therefore free from proteins, as the negative biuret reaction indicated, did not produce in rats any significant rise in percentage of reticulocytes.¹² Thus the active principle seems in some way bound to protein. Also, it has been shown that the reticulocyte response^{7,15,21,22} to antianemic principles is not specific, for increased percentages of reticulocytes have followed the administration of the various hormones and other nonspecific proteins.

The reticulocyte response is accordingly not an entirely reliable criterion for the determination of antianemic potency. It has seemed to us that the physiologic macrocytosis which occurs normally in most fetal mammals may serve as a test object for these principles governing hematopoiesis. The large red cells in the fetus rapidly reduce in size and volume after birth, owing perhaps to the fact that greater amounts of the antianemic principles are then available for red cell stimulation.

During development from birth to maturity the average diameter of the red blood cell in the white rat decreases from approximately 10 microns to about 6. Ordinarily, enlarged erythrocytes do not occur in the healthy adult, but in certain pathologic conditions involving liver damage macrocytoses have been described.¹⁰ Wintrobe and Shumacker³¹ observed the similarity between the fetal red blood cells and those of patients with pernicious anemia who were subjected to the influence of liver therapy. This similarity led Wintrobe and Shumacker to suggest that the essential antianemic principles which are required for the maturation of the red cells may not be available in adequate amounts, either in fetal blood or in the blood of patients with pernicious anemia.

If maturation of the red cell is a function of the antianemic principle in gastric juice, it seems reasonable to conclude that augmenting the maternal stores during pregnancy might induce changes in the size and volume of the fetal red cells. Stimulation of erythropoiesis in the fetus is thought to be a function of the antianemic principle of the mother. Certainly there is no conclusive evidence that the fetus elaborates its own principle. Extracts of fetal liver² and of placenta³² have proved ineffective in producing reticulocyte responses. Wigodsky, Richter and Ivy²⁸ have recently reported excellent results with an extract prepared from fetal calves' liver. They secured a reticulocytosis of 49% in patients who were in severe relapse with pernicious anemia. There is no evidence to indicate that the developing fetal gastro-intestinal tract elaborates any substances which have hematopoietic potencies.

This report covers the results of our study, in which we have injected concentrated gastric juice of man and of hog into pregnant rats during a part of the period of gestation and have then studied the red blood cells of the young rats at birth.

Materials and Methods. Samples of gastric juice were obtained, following test meals or the administration of histamine, from healthy persons from the Section on Gastro-enterology at The Mayo Clinic. These samples were filtered, pooled, concentrated to one-tenth their original volume and stored in the refrigerator. Before use these samples were neutralized with sodium hydroxide.

Samples of gastric juice free of food factors were obtained from a fundic pouch prepared in the stomach of a young hog, weighing 40 pounds. The pouch was drained by a Pezzar catheter, connected to a rubber balloon. Gastric juice was removed from the balloon 3 times daily, pooled, concentrated and neutralized as were the human samples. All samples of gastric juice used gave a positive biuret reaction.

Samples of gastric juice, both human and hog, which were used for control injections, were heated to 100° C. for 15 minutes.

One cubic centimeter of the concentrated gastric juice, the normal or the heated, was injected daily into the peritoneal space of rats during a part or all of the gestation period. Seventeen pregnant rats received 1 cc. daily of concentrated human gastric juice. Of these, 5 received injections on the 4 days immediately preceding parturition, 5 received injections on the 6 days immediately preceding parturition, and 4 received injections on the

12 days immediately preceding parturition. Three pregnant rats received 1 cc. of the heated gastric juice on each of the 8 days immediately preceding parturition.

Fifteen pregnant rats received 1 cc. daily of concentrated hog gastric juice obtained from the fundic pouch. Of these, 4 rats received injections on the 4 consecutive days preceding parturition, 5 received injections on each of the 7 consecutive days preceding parturition and 2 received injections on each of the 10 days preceding parturition. Four pregnant rats, serving as controls, received injections on the 4 consecutive days preceding delivery, of 1 cc. of the concentrated hog gastric juice which had been heated to 100° C. for 15 minutes.

At birth, blood was taken by cardiac puncture from each newborn rat. The total number of red cells per c.mm. was determined, using standard pipets. Using heparin as an anticoagulant, the percentage of red cells of whole blood was computed. Hematocrit tubes (Van Allen's type) were centrifuged for 15 minutes at 2400 revolutions per minute. Smears were stained with Wright's stain and the red cells were measured directly in microns from photographs made of these smears at 1000 diameters on photosensitized paper. One hundred cells from the blood of each newborn rat were measured. Cell volumes were computed according to the method of Wintrobe.³⁰

Results. The data assembled from the study of the blood of newborn rats the mothers of which had received human gastric juice show that human gastric juice contains some principle which when injected into pregnant rats has a definite effect upon the size and volume of the red blood cells of the developing fetus (Table 1). There were slight increases from normal levels in the number of red cells per c.mm. of fluid, decreases in the percentage of packed red cells and decreases in the largest diameters as well as in the volumes of the red cells. In general, the most marked changes were observed in those newborn rats born of mothers which had received an injection each day for the last 12 days of pregnancy. The curves (Price-Jones curves) depicting the percentage distribution of the sizes of the red blood cells in normal rats and in those born of mothers which had received 12 injections of gastric juice are shown (Fig. 1).

The red cells in mature rats of our strain measured 6.1 microns in average diameter, which is just 4 microns less than the average diameter of the red cells of their normal young at birth. The average diameter of cells of rats born of mothers which had received 12 injections was 8.5 microns, or 1.5 micron less than the normal diameter at birth. The decrease in the average diameter of red cells of newborn rats produced by 12 injections of gastric juice into the mother is therefore about 39% of the total decrease in size of red cells which occurs during the entire postnatal development.

When gastric juice was heated to 100° C. for 15 minutes and then injected into pregnant animals, there were no significant effects on the size or volume of the red cells in the offspring (Table 1).

The data on the blood of newborn rats born to mothers which had received the gastric juice from the fundic pouch of the hog (Table 2)

resemble those observed following the administration of human gastric juice, and show that there is present in the hog gastric juice, as in that of man, some substance which hastens maturation of the red cells (Table 1). The effect was proportional to the amount of concentrated juice given the mother. The decrease in the average red cell size in young born to mothers receiving 10 daily injections was about 31% of the total decrease in size which normally occurs during the interval from birth to maturity.

TABLE 1.—EFFECT OF INTRAPERITONEAL INJECTION OF 1 CC. OF CONCENTRATED HUMAN GASTRIC JUICE INTO PREGNANT RATS ON THE SIZE AND VOLUME OF THE ERYTHROCYTES OF THEIR OFFSPRING AT BIRTH OR SHORTLY AFTERWARD.

Daily injections into mother rat.	Newborn animals.	Volume of packed red cells, cc. per 100 cc. of blood.	Erythrocytes.		
			Number per c.mm., millions.	Largest diameter, microns.	Mean volume, cu. microns.
0	20	43.7 \pm 0.98 (39.0 — 53.0)	2.89 \pm 0.07 (2.00 — 3.42)	10.09 \pm 0.12 (9.67 — 10.79)	151.2
4	25	41.0 \pm 0.39 (39.0 — 44.0)	2.81 \pm 0.09 (2.25 — 3.19)	9.12 \pm 0.09 (8.45 — 9.47)	145.9
6	22	37.3 \pm 0.54 (32.0 — 47.0)	3.21 \pm 0.05 (2.87 — 3.79)	8.84 \pm 0.05 (8.25 — 9.39)	116.2
12	24	39.5 \pm 0.77 (37.0 — 45.0)	3.31 \pm 0.07 (3.10 — 3.50)	8.54 \pm 0.07 (7.93 — 8.98)	119.3
8*	20	41.3 \pm 0.53 (34.0 — 46.0)	2.69 \pm 0.07 (2.30 — 3.20)	10.01 \pm 0.05 (9.82 — 10.19)	153.5

* Inactivated gastric juice was injected.

TABLE 2.—EFFECT OF INTRAPERITONEAL INJECTION OF 1 CC. OF CONCENTRATED HOG GASTRIC JUICE INTO PREGNANT RATS ON THE SIZE AND VOLUME OF THE ERYTHROCYTES OF THEIR OFFSPRING AT BIRTH OR SHORTLY AFTERWARD.

Daily injections into mother rat.	Newborn animals.	Volume of packed red cells, cc. per 100 cc. of blood.	Erythrocytes.		
			Number per c.mm., millions.	Largest diameter, microns.	Mean volume, cu. microns.
0	20	43.7 \pm 0.98 (39.0 — 53.0)	2.89 \pm 0.07 (2.00 — 3.42)	10.09 \pm 0.12 (9.67 — 10.79)	151.2
4	24	41.4 \pm 0.34 (38.0 — 45.0)	2.89 \pm 0.06 (2.40 — 3.58)	9.16 \pm 0.05 (8.57 — 9.85)	143.7
7	28	40.6 \pm 0.66 (32.0 — 46.0)	3.07 \pm 0.07 (2.34 — 3.80)	8.93 \pm 0.06 (8.15 — 9.59)	133.7
10	7	38.7 \pm 0.68 (36.0 — 43.0)	3.21 \pm 0.04 (3.00 — 3.50)	8.84 \pm 0.11 (8.52 — 9.47)	120.6
4*	16	41.8 \pm 0.67 (36.0 — 49.0)	2.82 \pm 0.05 (2.08 — 3.40)	9.73 \pm 0.05 (9.32 — 10.21)	150.2

* Inactivated gastric juice was injected.

Comment. Gastric juice obtained from man or from the fundic pouch of a hog has been shown to contain some substance which accelerates the maturation of the red blood cells in the developing white rat. This acceleration was demonstrated in the blood of newborn rats by changes in the size and volume of their red cells. This substance in gastric juice is thermolabile, for when the samples of gastric juice were heated before its administration to pregnant rats, no changes in size or volume of the red cells in the young at the time of birth were observed. The effect induced in the red cells of the young rats was proportional to the number of injections of

gastric juice given the pregnant rat, for decreases from normal levels in both size and volume of the red cells were larger in those rats born to mothers which had received the daily injections of gastric juice for longer periods of time.

The physiologic macrocytosis of the newborn rat resembles the pathologic macrocytosis of certain anemias in that both conditions respond to treatment with the antianemic principle. It may be that the principle in gastric juice which reduces the normal physiologic macrocytosis of the newborn rat is identical with or a part of the antianemic principle in liver which is effective in producing remissions of certain macrocytic anemias. Castle and Ham⁴ have concluded that the antianemic principle which is stored in the liver is formed by the interaction of a factor in the diet with a factor in the gastric juice. Thus far our data on the effect of liver extract on the normal macrocytosis of young rats are incomplete, but indicate that some reduction in the size of the red cell in the newborn follows the administration of liver extract to the adult rat during gestation. Wigodsky and Ivy,²⁷ on the other hand, concluded that the erythrocyte picture of newborn rats, born to mothers which were treated with liver extracts of known antipernicious anemia potency, was not significantly different from that of untreated controls. Wintrobe, Kinsey, Blount and Trager³² did not observe any effect on the red blood cells of fetal rabbits from injecting liver extract into the mothers intramuscularly twice weekly. These authors likewise injected liver extract directly into the placenta at laparotomy. No significant changes were induced in the red cells of the fetus 13 days later at hysterectomy.

The extent of the physiologic macrocytosis which occurs in the blood of newborn animals varies greatly even within a given litter. This suggests that the amount of antianemic principle which is available to the fetus during development may vary from day to day. In all probability the source for the antianemic principle is the mother. There are no data to indicate that the fetus elaborates its own principle, for the extrinsic factor is probably absent and our knowledge concerning the elaboration of the intrinsic factor by the fetal stomach is incomplete. Briese³ concluded from her study of macrocytosis in newborn rats, the offspring of mothers treated with carbon tetrachloride, that the pathologic condition induced by the drug in the maternal liver seriously restricts the amounts of antianemic principle available to the fetus. This further indicates that the fetus depends on the stores in the maternal liver for its antianemic principle. As these stores are reduced in amount, owing to the cirrhotic condition of the liver, the degree of fetal macrocytosis seems to increase. Recently Parsons and co-workers¹⁷ studied the effect of diets deficient in iron on the size of the red cells in rats and they observed a microcytic hypochromic anemia in the offspring of these rats.

It is of interest that human and hog gastric juice proved equally effective in producing changes in the sizes and volumes of the red cells of newborn rats. Obviously human gastric juice, taken after test meals or histamine injections, included both intrinsic and extrinsic factors in its composition. But hog gastric juice removed by catheter from a separate pouch was necessarily devoid of any food factor and thus contained essentially the intrinsic factor only. However, it is possible that secretions from such a pouch may contain substances like the extrinsic factor, which are derived from gastric mucosa. An investigation of this possibility was beyond the scope of our present study. In both samples of gastric juice the active substances were thermolabile, so that we are inclined to believe that

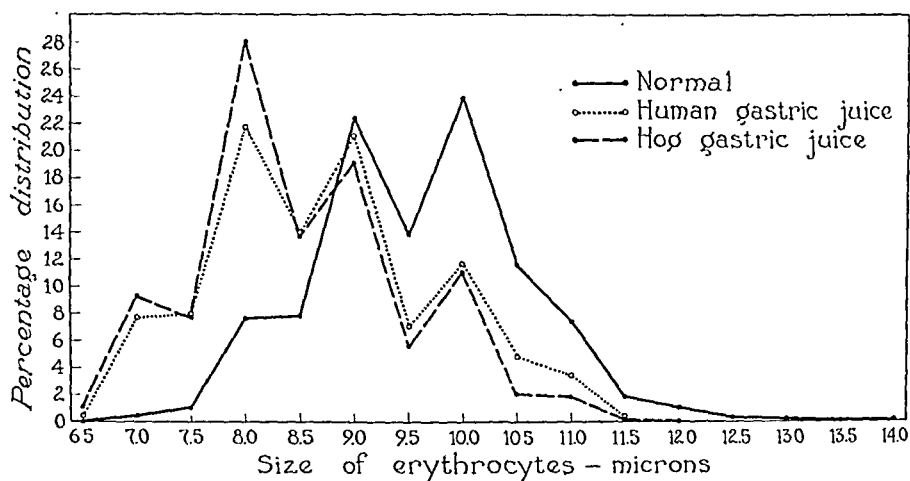


FIG. 1.—Percentage distribution, according to size, of the erythrocytes of rats born of untreated mothers, of mothers who had received human gastric juice for the last 12 days of pregnancy and of mothers who had received hog gastric juice for the last 10 days of pregnancy.

this principle, found in gastric juice, which reduces the size of red cells is either identical with the intrinsic principle of Castle or related to it.

No adequate bio-assay of the antianemic principle has yet been described. The reticulocyte response has been employed but there are serious objections to its use. In the first place the response is nonspecific, for rises in reticulocyte percentages may be obtained in response to all sorts of substances.^{12,21} And in the second place normal animals often show spontaneous unpredictable elevations in percentage of reticulocytes, so that any interpretation of results following the administration of antianemic substance is difficult.⁷ It is suggested that changes in the size of the red cell of the fetal or newborn rat may be a means of assaying antianemic potency of substances. The reaction is definite and the extent of the decrease

in size of the cells seems correlated with the amount of the principle administered. More experimental investigations are necessary to test the reliability of this method for bio-assay.

Summary and Conclusions. Concentrated samples of human and hog gastric juice have been administered daily to pregnant rats during a part of the gestation period. A study of the blood (obtained by cardiopuncture) of the young rats born to these adults has been made as soon after parturition as possible. Observations were made on the total number of red cells per c.mm., the volume of packed cells per 100 cc. of blood, the greatest diameter of the red cells and the volumes of the red cells. These data have been contrasted with comparable data obtained from young rats born to mothers which received inactivated samples of gastric juice and also with data obtained from young born to untreated normal adults. The following conclusions have been made:

1. Human gastric juice, obtained after test meal or histamine injection, and hog gastric juice, obtained from a fundic pouch, contain a substance which, when administered to the pregnant adult rat, accelerates the reduction in the size and volume of the developing red blood cells of the newborn rat. This substance causes: an increase in the number of red cells per c.mm. of fluid; a decrease in the percentage of packed red cells; a decrease in the greatest diameter of the red cells, and a decrease in the volume of the red cells.

2. These changes induced in the red cells of the newborn rat are, as a rule, proportional to the amount of gastric juice administered to the adult rat during gestation.

3. Heating samples of gastric juice renders the substance ineffective.

4. The physiologic macrocytosis which occurs normally in mammalian fetuses may be due to an inadequate amount of the anti-anemic principle, which is provided by the mother.

5. This effect upon the size and volume of red blood cells may prove to be a means of assaying the potency of antianemic principle.

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REPORT OF A CASE OF APLASTIC ANEMIA FOLLOWING GOLD INJECTIONS IN WHICH RECOVERY OCCURRED.

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SINCE the introduction of gold compounds for the treatment of tuberculosis, arthritis and lupus erythematosus, a number of reports have indicated that many hazards⁶ attend this type of treatment. These include immediate reactions such as syncope, nausea, edema of the lips and face, headache, malaise, chills and fever; and delayed toxic effects. The latter may appear a few hours after the administration of gold or may not be observed for several weeks. They result from involvement of the skin, mucous membranes, kidneys, liver or other organs, as well as the hematopoietic system, and may be very serious in their consequences.

The blood changes which have been observed following the use of gold are similar to those which are now well recognized accidents associated with the use of the organic arsenicals. As with the latter, these hematopoietic effects are extremely rare in comparison to the number of times the drug is administered. In the summary by Dameshek⁵ of cases reported until 1933, 1 case of purpura hemorrhagica, 1 of granulocytopenia, 5 of aplastic anemia, and 1 of "hypoplastic" anemia are included. From the discussion of these case reports it is evident that a few additional cases of similar character have been observed but have not been reported. Émile-Weil and Bousser⁸ referred to 30 instances of "hemorrhagic accidents" following the use of gold but the exact nature of these reactions was not given.

A number of reports have appeared since Dameshek's review in 1933. Like those reported before 1933, these have come chiefly from France where gold treatment has attained its widest popularity. The cases are classed under a great variety of diagnoses but we have divided them into 3 groups in accordance with criteria which are now generally accepted; namely, "aplastic anemia" when red blood corpuscles, leukocytes of the myeloid series and platelets are diminished in number; "granulocytopenia," when only the leukocytes are affected; and "purpura hemorrhagica" when platelets are reduced in number and any accompanying anemia can be accounted for by blood loss resulting from hemorrhages. In such cases there may be leukocytosis. This classification does not deny the possibility that the three types of blood disorder represent different degrees of injury of the same fundamental character.

According to these criteria, 6 cases of aplastic anemia,^{7,9,19,23,41,42} 9 cases of granulocytopenia,^{3,4,12,14,28,32,40} and 6 of purpura hemorrhagica,^{12,16,18,34,39} may be added to those listed by Dameshek. With the latter's case of aplastic anemia this makes a total of 13 cases of aplastic anemia, 10 of granulocytopenia, and 7 of purpura hemorrhagica, a total of 28 cases in all.

In 8 of the 10 cases of granulocytopenia and in 3 of the 7 cases of purpura which have developed following injections of gold, recovery occurred; but when the injury was such that anemia, granulocytopenia and thrombocytopenia developed, the result was usually fatal.

We have been able to find only 2 adequately described cases of aplastic anemia following gold therapy in which recovery occurred. Jullien's patient¹⁹ received a total of 6 gm. of crisalbine during a period of 3 months for the treatment of pulmonary tuberculosis. Shortly afterwards the red cell count was found to be 2,380,000, the hemoglobin 65%, the leukocytes 1550 and 81% of the latter were of the lymphoid series. The platelet count was not recorded but bleeding from the nose and uterus, and retinal hemorrhages occurred. The erythrocyte count fell as low as 1,760,000; the leukocytes to 930. Blood transfusions and Roentgen ray therapy were given. Seven months after anemia was first observed, the erythrocyte count was 3,850,000, the hemoglobin 75% and the leukocytes 5890, of which only 49% were lymphocytes. The patient was symptomatically well.

In the case described by Weissenbach, *et al.*⁴² it was not shown that the blood could be maintained at a satisfactory level without frequent repetition of blood transfusions. This patient had been given two courses of treatment for chronic infectious arthritis, receiving a total of 1.5 gm. of gold and sodium thiopropanol sulphionate in the first course and 2.0 gm. in the second, which was commenced after a rest period of 2 months. At the end of the second course a fleeting erythematous eruption appeared, weakness and purpura developed, and severe anemia of the aplastic type was

discovered. The erythrocyte count fell as low as 672,000 per c.mm. and the leukocytes numbered 800 per c.mm. Bleeding time was greatly prolonged. One year later, the patient was still alive, the erythrocyte count was 4,110,000 and the leukocytes ranged between 2000 and 5000 with 47 to 56% polymorphonuclears. The patient had received 50 blood transfusions and sodium nucleinate, pentnucleotide and liver extract had been used as well. In discussing Weissenbach's report, Rist referred to a patient of his own with aplastic anemia following gold therapy who had "recovered" but gave no details.

The following patient developed severe aplastic anemia while receiving gold injections and is alive and symptomatically well almost 4 years after the onset of anemia. Although her blood cannot be regarded as perfectly normal, she is able to maintain it at a satisfactory level even though she has had no blood transfusion nor other form of treatment for $2\frac{1}{2}$ years. She had been given a total of 230 mg. gold and sodium thiosulphate. She received a total of 9 blood transfusions and 17 months after the onset of aplastic anemia hysterectomy was carried out with the object of removing this source of blood loss.

Case Report. L. G., U-53639, a white woman, aged 34, came to the Skin Clinic of this hospital because of an eruption on her nose and face. She had been seen in the gynecologic clinic 6 months before where the hemoglobin was found to be 92%, the leukocytes numbered 13,500 and there were 72% neutrophils. On examination a series of well defined infiltrated plaques, which were subacutely inflamed and covered by slightly adherent scales, were present on the face, extending from the right mastoid prominence across the bridge of the nose to the malar process on the left. Small lesions were present on the scalp, behind the right ear and on the chest. This was diagnosed as lupus erythematosus (subsequently confirmed by biopsy). On August 17, 1934, 10 mg. of gold sodium thiosulphate were injected intravenously. For the next 2 weeks the same dose was repeated each week, and on the fourth week, the dose was increased to 25 mg. weekly, this amount being given for 5 weeks. On October 11, 1934, following an increase of the dose to 50 mg., nausea and vomiting developed. By the next week slight dermatitis with marked pruritus was noted about the arms, especially on the flexor surfaces. The dose at this time was reduced to 25 mg. On October 24, there was anorexia and slight edema of the face especially about the eyelids, and it was noted that the eruption was more extensive. Severe diarrhea developed and the patient felt weak, ill and generally run down. Skin biopsy at this time showed acute disseminating lupus erythematosus. Gold sodium thiosulphate injections were immediately stopped. Weakness increased in severity, and about December 5, pruritus became more marked. Four days later, blood examination revealed: erythrocyte count 1,250,000, hemoglobin 5.3 gm., volume of packed red cells 15.7 cc., mean corpuscular volume 125 c. μ ., leukocyte count 4200 per c.mm., and platelet count 46,000 per c.mm. Differential count: myelocytes 1%, juvenile neutrophils 4, segmented neutrophils 46, eosinophils 2, lymphocytes 46, and monocytes 1%. There was very marked anisocytosis with many macrocytes and some oval forms, slight poikilocytosis, and no achromia. The smears were practically devoid of platelets. The bleeding time was 7 minutes.

The patient was admitted to the hospital on December 19. T. 99.2°, P. 96, R. 20, B. P. 110/54. Many small brown macules all over the body and dark

pigmentation in the folds of the skin, were noted. There was marked pallor. Ophthalmoscopic examination revealed numerous flame-shaped hemorrhages in both fundi. No petechial hemorrhages were found on the skin. General examination, including neurological, was negative. Four transfusions of 500 cc. each, as well as pentnucleotide, and iron and ammonium citrate were given.

Definite improvement followed the transfusions. The erythrocytes increased in number and their mean size was reduced to normal, although the leukocyte and thrombocyte counts were little changed (Fig. 1). When she was discharged on January 26, 1935, there remained a mottled, brownish pigmentation of the arms, trunk and face. The erythrocyte count was 3,290,000, leukocytes 3200, platelets 120,000.

The patient was readmitted to the hospital on February 6, because profuse uterine bleeding had developed 17 days after the previous menstrual period. This ceased after one transfusion and the patient was discharged.

Menorrhagia recurred 1 month later. At this time the patient began to complain of a sensation of pins and needles in the limbs. Neurologic examination at this time and on many subsequent occasions failed to reveal changes in the nervous system other than a slight diminution of vibratory sense over the legs as high as the anterior superior iliac spines. Nevertheless, because of these symptoms and because repeated blood examinations revealed many macrocytes and a persistently high mean corpuscular volume, she was admitted to the hospital for the third time on June 13 for further study. Gastric analysis following the injection of histamine showed hydrochloric acid, free 22, combined 17. During the next month the patient was given 7 doses of liver extract (Lilly, 10 cc.). This therapy was associated with only a slight fluctuation in reticulocytes (from 0.75 to 2.90%) and the erythrocyte count did not change. The administration of sodium cacodylate (6 doses of 0.05 gm. intravenously) was associated with a similar fluctuation in reticulocytes. On July 19, 1935 a biopsy of the marrow of the tibia revealed fatty marrow for the most part, and the majority (84%) of the cells found there were lymphocytes. No nucleated red cells were seen (Table 1). Two more transfusions were given and the patient was discharged. Her condition had not been changed by liver therapy but following the transfusions the menorrhagia was less severe.

TABLE 1.—DIFFERENTIAL COUNTS OF BONE MARROW SMEARS.

	Sternum normal %	Tibia 7/19/35 %	Sternum 2/13/36 %	Sternum 6/15/38 %	Sternum 3/15/39 %
WBC					
Myeloblasts	2.0	..	3.0	0.3	1.0
Undiff. myelocytes	5.0	..	4.0	3.3	2.3
Diff. Myel. neutro.	12.0	..	8.0	21.0	23.3
eosin.	1.5	..	4.5	1.3
baso.	0.3				
Metamyelocytes neutro.	22.0	2	14.0	23.4	30.7
eosin.	2.0	0.7
PMN neutrophils	20.0	13	8.0	12.7	18.3
eosinophils	2.0	..	0.5	0.7
basophils	0.2				
Lymphocytes	10.0	84	42.5	24.3	11.0
Plasma cells	0.4	1.3	
Monocytes	2.0	1	1.5	2.0	1.0
Macrophages and reticulum cells	0.2	..	1.5	1.3	0.3
Megakaryocytes	0.4	0.4	
RBC					
Primitive erythroblasts and mac- roblasts	4.0	..	2.0	0.3	1.7
Normoblasts	18.0	..	8.0	9.7	7.7
Reticulocytes	5.0			5.2	1.5

Except for moderate weakness the patient had few complaints. On February 13, 1936, she was admitted for the fourth time and a sternal marrow biopsy was done. The marrow showed a few fatty aplastic areas interspersed among other areas of active hematopoiesis. The differential count of smears made from the marrow (Table 1) showed much more than the normal number of lymphocytes, with reduction in the neutrophilic myeloid cells, no megaloblasts, few macroblasts, and a few normoblasts.

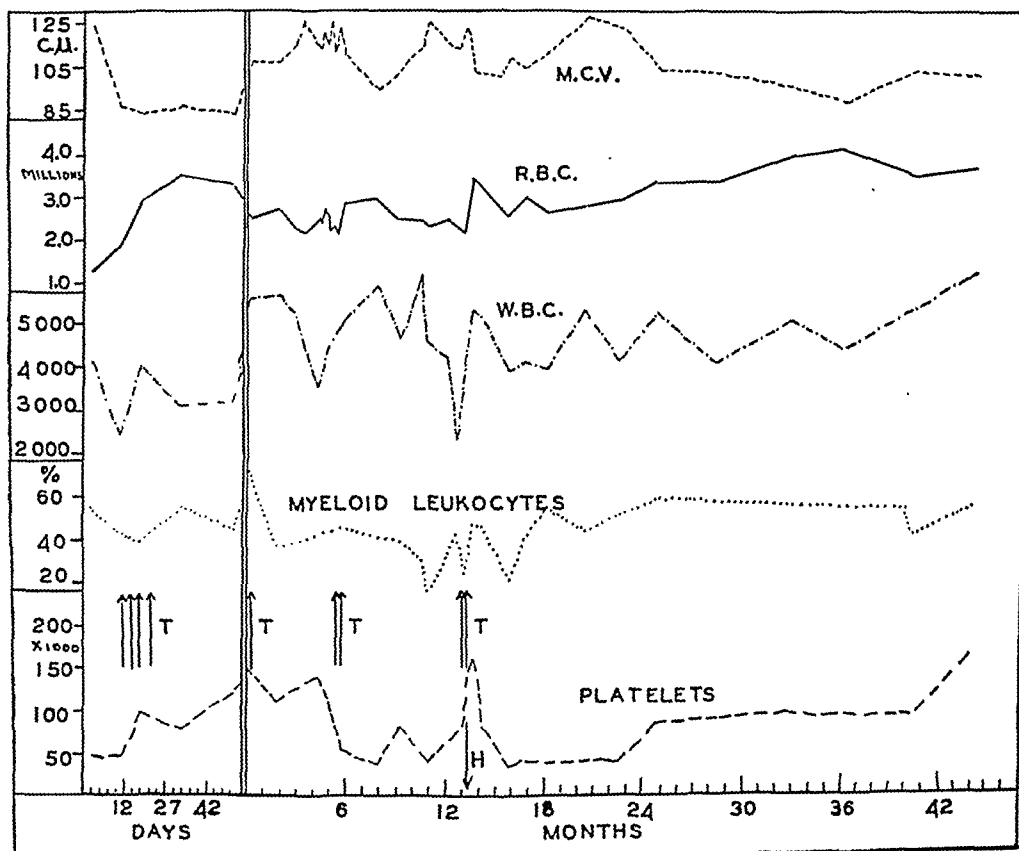


FIG. 1.—Changes in the blood of a case of aplastic anemia following the intravenous injection of gold sodium thiosulphate, the observations cover a period of 4 years.

M. C. V. refers to mean corpuscular volume, R. B. C. to red cell count and W. B. C. to white cell count. The arrows pointing upwards and marked "T" indicate transfusions and the arrow pointing downwards and marked "H" indicates the time of hysterectomy.

Treatment of the anemia was attempted again. However, injections of a fetal liver extract, ascorbic acid, and commercial liver extract were followed by no significant blood changes. On March 6 the erythrocyte count was 2,200,000, hemoglobin 9.3 gm., volume of packed red cells 26.9 cc., mean corpuscular volume 122 c.μ., platelets 80,000, leukocytes 3800 and neutrophils 23%. Hysterectomy was then performed (March 13) with the object of removing this source of blood loss, even though menorrhagia was no longer very severe. The operation was borne without mishap. Two transfusions were given before operation. Six days after operation the erythrocyte count was 3,410,000, hemoglobin 12.0 gm., volume of packed red cells 34.9 cc., platelets 166,000, leukocytes 5350 with 43% segmented and juvenile neutrophils. She was discharged a week later in good condition.

Since March 11, 1936, no further blood transfusions have been given. During the next year the patient continued to be well, complaining only of slight weakness and occasional sensations of numbness and tingling in her fingers and occasional swaying or stumbling on walking. On March 3, 1937, some diminution in vibratory sense in the legs was noted but the neurologic examination was otherwise normal. A tourniquet test showed numerous fine petechiæ.

A sternal marrow puncture was done on June 15, 1938. The specimen was quite cellular and showed that the lymphocytosis observed 2 years before had almost disappeared, the percentage having dropped to 24, while the myeloid leukocytes were much more numerous than they had been (Table 1). Nucleated red corpuscles were still somewhat reduced in number. No megaloblasts were found. The erythrocyte count of the blood at this time was 3,580,000, the hemoglobin 12.6 gm., the volume of packed red cells 38.0 cc., the mean corpuscular volume 103 c.µ., and occasional macrocytes were found in the blood smear. The platelet count was 91,000, although bleeding time was only 5 minutes, and clot retraction was complete in 1 hour. Relative lymphocytosis (52%) was still present. Symptomatically, the patient was well and able to carry on her housework. Her only complaint was of occasional pain in the back which is considered to be of arthritic origin.

The most recent examination of the patient was made on September 28, 1938, almost 4 years after the onset of her anemia. In spite of the fact that no blood transfusions had been given for 2½ years, the erythrocyte count remained at 3,660,000, the hemoglobin 12.6 gm., and the leukocytes numbered 6200 of which only 41% were lymphocytes. It is noteworthy that macrocytosis was still present, as indicated by the mean corpuscular volume of 100 c.µ., and the presence of macrocytes in the blood smear. Platelets were moderately plentiful in the blood smear and numbered 157,000 by count. Bleeding time was 5 minutes, coagulation time 13 minutes and the clot retracted in 1½ hours.*

Discussion. *Relation of Gold Injections to Aplastic Anemia.* The evidence that the injection of gold compounds is the cause of the hematopoietic changes which occasionally follow its use is only circumstantial. In our own case, the possibility must be considered that the blood changes observed were caused by the disease for which gold treatment was given, namely lupus erythematosus. Few adequate blood studies in cases of this disease are available. The most common change in the blood, when one occurs at all, seems to be leukopenia.²⁷ One of Templeton's³⁷ patients, however, had aplastic anemia even though gold therapy was not given. Two others were reported by him as having thrombocytopenia but in one of these the blood studies were inadequate, while in the other tuberculosis of the spleen might have accounted for the blood changes noted.

Incrimination of gold preparations as a cause of hematopoietic changes is made more plausible by the fact that similar changes are sometimes found following the injection of organic arsenicals. As with the latter, it seems impossible to predict whether in any given case untoward effects on the hematopoietic system are likely to occur. There is no correlation between the amount of gold given

* On reëxamination on March 15, 1939, the blood findings were essentially the same except that the platelet count had risen still further and numerous platelets were found in the blood smear.

or the duration of the treatment and toxic effects. Rist, in discussing the case of Weissenbach, *et al.*,⁴² referred to a patient who received 45 gm. of crysalbine (sodium and gold thiosulphate) with no apparent harmful results. Some form of hypersensitiveness is probably the underlying disorder.

Attempts to produce blood changes in animals by the injection of heavy metals have, with a few unconvincing exceptions, been unsuccessful. Émile-Weil and Bousser⁸ produced retardation of coagulation of the blood of rabbits by the injection of Solganol, a gold salt. Bernard,² using crysalbine (gold and sodium thiosulphate) reported a 50% reduction of the platelet count and prolongation of bleeding time following injections into the femoral bone marrow of rats, but failed to produce changes by intravenous injections. Likewise Pan³¹ and Heinild¹⁵ failed to produce blood changes in rabbits by the injection of gold compounds and Shouse and Whipple³³ failed to do so by the injection of silver.

Our own attempts to produce blood changes in rabbits* by the intravenous injection of gold sodium thiosulphate have also been unsuccessful. One animal received four injections of 10 mg. each, another one injection of 50 mg., and a third nine injections of 50 mg. each over a period of 3 months. In the last 2 animals a slight reduction in the erythrocyte count followed the first injections of gold but this did not continue after subsequent injections, and no changes occurred in leukocytes or platelets.

Prognosis in Aplastic Anemia. Recovery following aplastic anemia is extremely unusual. Among the reported cases of "idiopathic" aplastic anemia, we have found an account of only 6 patients who lived more than a year after the onset of the anemia and even these cannot be considered as having completely recovered. Gibson's¹⁰ patient, a girl aged 11 years, received daily injections of adrenalin for 6 years and remained symptomatically well although moderate anemia and leukopenia persisted. She died at the end of this time of hemorrhagic chicken-pox. Upham and Nelson³⁸ reported a case in which fetal liver feeding was associated with such improvement that the patient was still alive 2 years after the onset of the anemia. It is noteworthy that at the end of that time thrombocytopenia and moderate anemia were still present. Harrison's¹¹ patient was treated with 290 transfusions and died after 9 years of a delayed transfusion reaction.²¹ This man was found to have hemochromatosis. A patient of Osato *et al.*³⁰ (Case VIII), after repeated blood transfusions and radiation of the long bones, was no longer anemic 22 months after anemia was first observed, but moderate leukopenia and thrombocytopenia still persisted. Another patient (Case VIII) showed moderate anemia, leukopenia and thrombocytopenia after 1 year. Atwood's patient,¹ a boy aged 12 years, whose red cell count fell as low as 970,000, after only 2 blood transfusions and administration of adrenalin and ephedrine, was found

* Aided by funds from a Parke, Davis & Co. grant for studies in hematology.

to be quite normal at the end of a year, with a leukocyte count of 4350 as the only indication of hematopoietic deficiency.

In cases of aplastic anemia following injection of the arsphenamines, prognosis is slightly more favorable. Of the 34 cases collected by McCarthy and Wilson²⁶ 6 (18%) were said to have recovered. Two of these cases (1 and 4), however, did not show a completely typical picture of aplastic anemia and one of them (Case 5) was still very anemic at the time of the report. Thus the proportion of recovered cases is reduced possibly to 9 or 10%. It is very difficult to discover what is the true mortality in cases of post-arsenical aplastic anemia from examination of case reports because cases in which recovery occurred are more likely to be reported than fatalities. Kadin²⁰ recently collected 17 cases of aplastic anemia following the use of arsenicals and added 3 of his own. This series includes 6 patients who made partial^{22,25,27} or complete^{17,35,36} recovery. Hawkins¹³ reported a case in which recovery occurred and Lieberman and Weiss²⁴ have lately reported 2 more cases. Thus a total of about 13 patients have been reported as making complete or partial recovery following aplastic anemia caused by the injection of one of the organic arsenicals. One of the patients admitted to this hospital with post-arsenical aplastic anemia has improved.

The rarity of recovery in cases of aplastic anemia following gold injections has already been mentioned. Although the patient we have described is now symptomatically well 4 years following the onset of anemia, her blood is not entirely normal. The persisting macrocytosis is of considerable interest. With the failure of intensive liver therapy to affect the blood and the lack of achlorhydria, an Addisonian type of anemia can be ruled out. Elsewhere⁴³ one of us pointed out that macrocytosis may be associated with extra-medullary blood formation. One wonders whether the development extra-medullary blood forming tissue may account not only for the macrocytosis in this case but also in part for the patient's recovery.

Summary. 1. A case of aplastic anemia, presumably due to the intravenous injection of a gold compound, is reported.

2. This patient is still alive 4 years after the development of aplastic anemia and is symptomatically well although the blood is not entirely normal. She has had no transfusions for 3 years.

3. The case reports of harmful hematopoietic effects following the use of gold are briefly reviewed, especially from the standpoint of prognosis. The reported case is the third of a total of 13 cases of aplastic anemia in which death had not occurred at the time of the report and is the second one which has attained almost complete recovery.

4. Experiments are mentioned in which attempts to produce changes in the blood of rabbits by the intravenous injection of gold failed. The evidence incriminating gold as a cause of blood changes is entirely circumstantial.

5. The literature dealing with recovery in cases of idiopathic

aplastic anemia and in cases following the injection of organic arsenicals, is reviewed. Only 6 of the former type have survived a year or longer while in the post-arsenical group 13 partial or complete recoveries have been recorded.

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PHAGOCYTIC ACTIVITY IN LEUKEMIA.*

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THE question of the infectious nature of leukemia has been discussed for many years. Because the various clinical manifestations of this disease often resemble an acute infectious process, it was assumed, for many years, that it might possibly have an infectious basis. Ordway⁴ has made an excellent summary of the work in this field. Pagniez⁵ reviewed the recent experimental work and concluded that leukemia was a disease of an infectious nature.

* This investigation was begun under the direction of the late Dr. Richard H. Jaffe.

The mature white cells in many forms of leukemia are apparently perfectly normal and should form the usual defense against infection. One might draw the conclusion that leukemia would probably have an infectious basis if the white cells are functioning in a normal manner. If the infection attacks the blood forming organs, then leukemia may result, and the few remaining normal mature cells are powerless to combat the overwhelming infection. If the mature cells which are present in leukemia are not functioning normally, they will not offer the usual defense against infection, the body will be exceedingly susceptible to infection and the usual infection associated with leukemia may be assumed to be superimposed upon an already weakened system. Howell³ has shown that leukemic individuals may fail to develop antibodies after infection or vaccination, probably as a result of the marked changes in the hematopoietic tissues found in leukemia.

This study of various types of leukemia was undertaken to shed some light on that problem. An attempt was made to determine the condition of the mature cells remaining in the leukemia patient and circulating in the peripheral blood stream. Strumia and Boerner⁷ have shown that the phagocytic activity of granulocytes increases proportionately with their age. Furthermore, this phagocytic power of white cells is a fair measure of their activity against bacteriologic infection. It was, therefore, decided to determine the phagocytic power of the mature white cells in the circulating blood of leukemic patients. In addition to this, complete bacteriologic studies of each patient were made, a rather complete history obtained, and the sedimentation rate of the red blood corpuscles was noted.

Bonanno¹ incubated 1 cc. of blood and 1 cc. of sodium citrate with a staphylococcus strain for 45 minutes at 37° C. He then made smears which he stained with methylene blue. He investigated 5 cases of chronic myeloid leukemia, 2 cases of chronic lymphatic leukemia and 1 case of hemocytoblastica. In his series of cases he found the phagocytic power was greatly reduced.

The present series consisted of 1 case of acute monocytic leukemia, 1 of acute aleukemic stem-cell leukemia, 3 of acute stem-cell leukemia, 3 of acute myelogenous leukemia, 2 of acute lymphatic leukemia, 1 of subacute aleukemic stem-cell leukemia, 5 of chronic myelogenous leukemia, and 4 of chronic lymphatic leukemia, a total of 20 cases. In addition, the blood of 20 individuals free from leukemia or infection was used as controls and the figures averaged.

The strain of staphylococcus used was readily phagocytized by normal blood but retained sufficient virulence so that only an average of 96% of the neutrophils of normal blood phagocytized the bacteria. The method of Strumia and Boerner⁷ was used to set up the test. Two-tenths of 1 cc. of a washed suspension of white cells was mixed with 0.1 cc. of the staphylococcus suspension (containing approximately 1 billion bacteria per cc.) and 0.1 cc. of a 1 to 10 dilution of fresh normal pooled serum. The mixture was shaken for

30 minutes. At the end of that time smears were made, stained with Wright stain and examined. The number of cells which showed phagocytic activity was noted. Also, the kind of cell and the number of bacteria per cell were counted. Because in many cases the number of mature neutrophils was very small, the figures are only accurate when compared with this number.

Bacteriologic studies were made on nose, throat, blood, urine and stool cultures and on any other material from the patient which seemed to be from an infected source. Anærobic and ærobic cultures were made.

A simple sedimentation test was done, using 2 parts of 2% sodium citrate to 8 parts of blood. (According to Cutler *et al.*,² simple sedimentation tests are not satisfactory. However, it was felt that for purposes of comparison a simple sedimentation test was sufficient, inasmuch as the same method was used throughout, and the same sources of error were present in each study.) The blood-citrate mixture was drawn into a tuberculin syringe, placed upright on a stand and the drop noted in time intervals of 1, 5, 10, 15, 30, 45, 60, 90 and 120 minutes, and after 18 to 24 hours. This, of course, gives only comparative sedimentation rates.

Results (Table 1). In no case did more than 70% of the mature leukocytes phagocytize the bacteria. When this figure is contrasted with the average of 96% for the controls, it will be readily seen that the phagocytic power of the leukemic blood was decreased. In certain cases only 30% of the leukocytes were active. The average number of bacteria per cell varied from 38.2 to 2.6 bacteria, as contrasted with 18 for the normals.

With few exceptions, bacteriologic findings seemed to be positive in the acute leukemias. That is, the individuals showed a predominance of one organism in all the cultures either with a positive blood culture, indicating sepsis, or without positive blood culture.

The acute monocytic leukemia of 3 weeks' duration showed 7% mature neutrophils; 64% of these showed phagocytic activity with an average of 6.6 bacteria per cell. The sedimentation rate was very fast and dropped suddenly after the first few minutes. The patient had an almost pure culture of *Strep. hemolyticus* in the throat.

The acute aleukemic stem-cell leukemia of 1 week's duration showed 67% normal mature neutrophils, 50% of which showed phagocytic activity with an average of 20 bacteria per cell. The sedimentation rate began to fall very slowly and then took a sudden drop. This patient showed anærobic *Strep. hemolyticus* in the blood cultures.

The subacute aleukemic stem-cell leukemia of 8 months' duration showed 34% mature neutrophils, 62% of which showed phagocytic activity with an average of 7 bacteria per cell. The sedimentation rate was normal and the bacteriologic studies negative.

Three cases of acute stem-cell leukemia, varying from 1 to 8 months' duration, showed varying numbers of mature neutrophils and the percentage of those which showed phagocytic activity varied

from 20 to 70%. The number of bacteria per cell varied from 8 to 22.6. Two of these bloods showed a slightly increased sedimentation rate in the first few minutes, followed by a sudden drop. The third fell very fast in the beginning, slowed up after 15 minutes and then took a sudden drop. In 1 of these cases *Strep. viridans* predominated in all the cultures; in another there was a *Strep. hemolyticus* blood culture; in the third, bacteriologic study was negative.

TABLE 1.—RESULTS OF STUDIES IN LEUKEMIC PATIENTS.

Age (yrs.).	Sex.	Race.	Duration.	Type of leukemia.	Red blood cells in millions.	White blood cells in thousands.	Mature neutrophils (per cent).	Phagocytes (per cent).	Average No. bacteria per cell.	Sedimentation rate.	Bacteria present.
24	F	W	3 wks.	Acute monocytic	3.4	105.7	7	64	6.6	Very fast and sudden drop	<i>Str. Hemolyticus</i> in throat.
49	M	W	1 wk.	Acute aleukemic stem-cell	1.2	29.2	67	50	20	Slow and then sudden	Anerobic <i>Str. hemolyticus</i> in blood culture.
51	M	W	8 mos.	Subacute aleukemic stem-cell	3.9	8.6	34	64	7	Normal	Negative.
40	F	N	8 mos.	Acute stem-cell	3.3	170	10	70	8.7	Very fast and sudden drop	<i>Str. viridans</i> predominant in all cultures.
57	M	W	4 wks.	Acute stem-cell	2.5	279.6	1+	5 polys counted 1 phagocyte (20%)	8	Slow and then sudden drop	<i>Str. hemolyticus</i> in blood culture and all other cultures.
16	M	W	1 mo.	Acute stem-cell	1.1	4.3	20	56	22.6	Slow then very sudden	Negative.
15	F	W	1 wk.	Acute myelogenous	1.1	272	9	43	3.7	Slow—fast, large drops, slow	<i>Str. viridans</i> in blood and all other cultures Vincent's angina.
51	F	W	2 wks.	Acute myelogenous	1.3	104	15	40	10	Very slow, average drops	<i>Sta. albus</i> in blood and all other cultures
23	F	N	3 mos.	Acute myelogenous	1.2	38.6	5	40	5.3	Slow, very sudden and large drop—slow	<i>B. mucosus</i> in all cultures.
23	M	W	2 yrs.	Chronic myelogenous	4.5	50.5	70	54	4	Normal	<i>Str. viridans</i> in blood culture and all other cultures.
40	M	W	2 yrs.	Chronic myelogenous	1.2	96	20	44	6.4	Normal (slow)	Negative.
51	F	N	2 yrs.	Chronic myelogenous	2.8	560	37	60	7.5	Normal (fast)	Negative.
33	F	W	?	Chronic myelogenous	2.3	52.8	10	47	6	Normal	Negative.
49	F	N	3 mos.	Chronic myelogenous	4.6	350	27	37	4.6	Very slow	<i>Str. viridans</i> in blood and ascites and all other cultures.
40	M	W	9 mos.	Acute lymphatic	1.3	8.6	23	70	38.2	Sudden drop slow	Negative.
6	M	N	3 wks.	Acute lymphatic	3.2	96.7	28	50	3	Normal	Negative.
57	M	W	1 yr.	Chronic lymphatic	3.1	83.8	52	30	3	Normal (fast)	<i>Str. hemolyticus</i> in blood and all other cultures.
55	M	W	3 yrs.	Chronic lymphatic	3.2	120	63	38	2.6	Normal (slow)	Negative.
65	M	W	6 mos.	Chronic lymphatic	2.9	14	35	51	22.19	Normal	Negative.
62	M	N	4 mos.	Chronic lymphatic	3.4	81.5	2	34	14.3	Normal	Negative.

The acute myelogenous leukemias of from 1 week to 3 months' duration showed from 5 to 15% mature neutrophils. The number of neutrophils showing phagocytic activity was around 40% in all 3 cases. The number of bacteria per cell varied from 3.7 to 10. The sedimentation rate was slow at the outset, followed by a fast, sudden and large drop and then a slow decrease. Each of the cases showed positive bacteriologic findings. In one of them, *Strep. viridans* was found in the blood culture as well as in all the other cultures and an acute Vincent's angina was present. The second patient showed *Staph. albus* in the blood culture and this organism predominated in all other cultures. In the third patient, Friedländer's bacillus predominated in all the cultures.

The 5 cases of chronic myelogenous leukemia varied from 3 months to 2 years' duration. The percentage of mature neutrophils varied from 10 to 70 and the phagocytic activity of these cells ranged from 37 to 60%. The average number of bacteria per cell varied from 4 to 7.5, a very small range. The sedimentation rate was normal in all 4 cases. One of these 4 showed *Strep. viridans* in a blood culture and predominating in all the other cultures. The fifth case showed a very fast sedimentation rate and *Strep. viridans* was isolated from all of the cultures, including the blood cultures and ascitic fluid cultures.

Two cases of acute lymphatic leukemia, one of 3 weeks' duration, showed approximately the same number of mature neutrophils: 28 and 23% respectively. Fifty per cent of the cells of the case of short duration showed phagocytic activity, with an average of 3 bacteria per cell. This was in marked contrast to the 70% of mature neutrophils in the case of longer duration which showed an average of 38.2 bacteria per cell. The sedimentation rate of this latter case dropped suddenly and then decreased slowly. The bacteriologic study in both cases was negative.

Four cases of chronic lymphatic leukemia, from 4 months to 3 years' duration, had from 30 to 51% of mature neutrophils showing phagocytic activity. The average number of bacteria per cell ranged from 3 to 22.19. The sedimentation rate in all 4 cases was normal, although one patient in a terminal state showed a very slightly increased rate. This patient also showed *Strep. hemolyticus* in the blood culture and other cultures. The bacteriologic findings in the other cases were negative.

These figures bring to light several very interesting facts. First of all they show that the sedimentation rate varies, as one would expect, with the duration and severity of the illness. In addition, those leukemic patients who seemed to be running a fairly slow, chronic course were, for the most part, free from systemic infection.

It is obvious that the percentage of mature neutrophils which showed phagocytic activity is considerably lower than normal. The average number of bacteria per cell was also lower than normal. It should be mentioned here that a few of the immature neutrophils phagocytized bacteria. This was especially marked in the acute

monocytic leukemia, but, for purposes of comparison, these figures were eliminated from the results. Strumia and Boerner⁷ have made an excellent study of the phagocytic activity of immature leukocytes.

Discussion. In his book on the sedimentation rate of red blood corpuscles, Reichel⁶ describes the factors which may influence this rate. Most of them were eliminated in this study. Since no attempt was made to secure an accurate sedimentation rate, all of the rates obtained are comparable. Every test was done in the same tuberculin syringe at room temperature (20° C.) within one-half hour after the blood was drawn. Reichel⁶ found an increased sedimentation rate in leukemia. It is, therefore, interesting to note that many of the chronic cases which were investigated in this study showed normal rates.

Concerning the bacteriologic studies, it appears that the chronic cases were quite free from severe bacterial infection. Perhaps that is the reason they are chronic cases. However, it seems more probable that because they are chronic they are more resistant to infection. All of the chronic cases showed a fairly high phagocytic activity. In those cases with positive bacteriologic findings it appears that the infection is superimposed upon the leukemia, possibly due to the decreased phagocytic activity.

It would seem, therefore, that leukemia is not an infectious disease; that the infection so often found in leukemia is superimposed upon that condition and may be due, in part, to the decreased resistance of the leukemic individuals, as evidenced by the decrease in the phagocytic activity of their blood.

Summary. 1. Phagocytic studies, sedimentation rates, and bacteriologic studies were made in 20 cases of various types of leukemia.

2. The number of mature neutrophils in the peripheral blood of leukemic individuals which showed phagocytic activity was greatly decreased from normal and the phagocytic activity of the existing cells was also greatly decreased.

3. The sedimentation rate was increased in most of the acute cases but was normal in most of the chronic cases of leukemia.

4. Significant bacteriologic findings were noted in most of the acute cases.

5. It seems probable that leukemia is not itself an infectious disease but that infection so often found associated with that disease is superimposed upon the leukemia.

6. This may be due to the decreased resistance of the leukemic individual, as evidenced by the decrease in phagocytic activity of the mature neutrophils.

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BOOK REVIEWS AND NOTICES.

MODERN SURGICAL TECHNIC. In 3 Volumes. Vol. 1. General Operative Considerations: Surgery of the Head and Neck, and Plastic Surgery. Vol. 2. Surgery of the Nerves, Vessels, Bone, Breast and Chest; Vol. 3. Abdominal Surgery, Hernia, Genito-Urinary and Gynecologic Surgery. By MAX THOREK, M.D., K.L.H. (FRANCE), K.C. (ITALY), Professor of Clinical Surgery, Cook County Graduate School of Medicine; Attending Surgeon, Cook County Hospital; Surgeon-in-Chief, The American Hospital, etc. With a Foreword by DONALD C. BALFOUR, M.B., M.D. (TOR.), LL.D., F.A.C.S., F.R.A.C.S., Head of Section in Division of Surgery, The Mayo Clinic; Director and Professor of Surgery, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, etc. Pp. 2045; 2174 illustrations, originals principally by W. C. Shepard. Philadelphia: J. B. Lippincott Company, 1938. Price, \$33 per set.

THE author has attempted to write an operative surgery intermediate in length between the long system and the single volume surgery. The book aims to contain enough surgical technique and a sufficiently detailed description of each commonly performed operation to be used by students and general surgeons and those general practitioners who are occasionally called upon to perform emergency operations. He has included sufficient anatomic details to acquaint the reader with the operative field, and he has used the step-by-step method in describing the operation.

Volume 1 is divided into two parts. In Part I. General Operative Considerations, the author describes the general relations of the surgeon to his art and to his patient and discusses in a relatively brief manner the set-up of the operating room, sterilization of the surgical supplies and the various types of anesthesia. His descriptions are those of his own technique in most part, and these probably are not always acceptable to the reader. For instance, the author illustrates and lays some stress upon the sealing of the umbilical pit with collodion in preparation for operation. This is not a procedure which is generally accepted in most clinics as being very valuable. His sections on the preoperative and postoperative complications are relatively brief.

In the chapter on anesthesia, the author unfortunately does not mention any of the newer anesthetic agents, such as vinethene and cyclopropane. He is not convinced that any of the spinal anesthetics, except novocaine, are of particular value. His section on regional anesthesia is brief but to the point.

Part II of Volume 1 is concerned with the surgery of the head and neck and plastic surgery. A relatively long chapter on the surgery of the skull and brain describes various surgical procedures in detail. This chapter is well illustrated and would be extremely useful for one who occasionally has to perform operations on this part of the body. The author surprisingly does not mention the use of 50% glucose intravenously in the control of increased intracranial tension, although he considers the use of hypertonic saline, magnesium sulphate and spinal puncture. The chapters on surgery of the ears and tonsils are well written and profusely illustrated. A considerable portion of one chapter is given over to a description of neurectomy of several facial nerves. It would appear that disproportionate space is given to this minor subject. The final chapters of the book include

descriptions of the surgery of the salivary glands, jaws, orbit and eye, and the surgery of the nose, neck and cervical endocrine glands. A brief and well-illustrated chapter on the general principles of plastic surgery finishes the first volume.

Volume 2: This volume is likewise divided into two parts. The first part is concerned with the surgery of the nerves, vessels and bones. In the chapter on peripheral nerves, such operations as neurolysis, anastomosis and operations for spastic paralysis are described and illustrated. The chapter on the surgery of the sympathetic nervous system is a mixture of old and new. The author describes the various operations which were advocated during the first years of sympathetic surgery, periarterial sympathectomy and so-called cervicothoracic sympathectomy. In discussing the latter operation, he does not mention the resection of the first, second and third thoracic ganglia which have been shown in recent publications to be the important sympathetic structures to be removed in sympathectomy of the upper extremities. He does not describe the Gask-Telford operation for anterior thoracic sympathectomy, nor the White-Smithwick or Adson technique for posterior sympathectomy. Included in this section are such operations as chordotomy and adrenal denervation as practised by Crile.

In the chapter on surgery of the vascular system, the operator gives well-illustrated sections on ligations of the arteries. His section on surgery of veins, however, does not include the more modern ideas concerning ligation of the saphenous vein. His section on aneurysms is good. He gives in great detail a discussion on blood transfusions with illustrations of innumerable types of transfusion apparatus.

The chapter on orthopedic surgery describes almost all of the commonly performed operations. Very little is mentioned about the subdeltoid bursa (here Codman's name is spelled Cadman). The author includes in this chapter, strangely enough, operations for meningocele and pilonidal sinus. The chapter on amputation is well written and very nicely illustrated. A rather long chapter on fractures and dislocations considers mostly the operative treatment of these lesions. Little is said concerning the more modern treatment of fractures with the use of various mechanical appliances for reduction. In discussing recurrent dislocations of the shoulder the author merely mentions the Nicola operation, although he describes in detail other operations which are less generally used. The last part of the volume concerns the surgery of the breast and chest. Here the author includes a fairly large section on his own methods of plastic surgery of the breast. A fairly complete outline of the various commonly accepted operations on the chest are described and well illustrated. The part is concluded by a chapter on the heart and pericardium, in which there is a good summary of the work of Claude Beck.

Volume 3, concerned with the surgery of the abdomen, is divided into two parts. First is the surgery of the abdomen and the abdominal organs and, second, surgery of the pelvic region. The first part includes a discussion of the various commonly used procedures in dealing with diseases of the stomach, intestines, liver, pancreas, spleen and hernia. These sections are well written and the author is evidently writing from a mass of clinical experience. He has illustrated the text profusely and in most cases with diagrammatic illustrations which increase the clarity of the text. The chapter on the surgery of the pelvic regions concerns the commoner gynecologic operations in a relatively brief manner, and perhaps more fully discusses the operations upon the kidney, bladder, prostate and external genitalia.

In reviewing these 3 volumes, one is impressed by the mass of material which is included in them, and is not surprised that there may be some

things left out which would appear important to individual readers. On the whole, the book serves a very useful purpose for those who are interested in obtaining a rapid and concise review of the methods of performing various surgical operations. The text is concisely written and perhaps a little too rigidly adheres to the step-by-step method, although the advantage of this type of text for beginners is evident. The illustrations as a whole are well done. The author has included in his list more operations proposed and performed by European surgeons than would seem justifiable. By the same token, he has omitted a considerable amount of original work which can be found in the American literature.

The Reviewer is glad to have these volumes to add to his library and he is certain to use them frequently. They should be a part of the library of most operating surgeons and especially of those who occasionally operate and wish to have an authoritative volume to which they may turn for rapid reference.

L. F.

OUT OF THE RUNNING. By G. GERTRUDE HOOPES. With a Foreword by EDGAR A. DOLL, PH.D., Director of the Department of Research, The Training School at Vineland, N. J., and with Clinical Notes by WINTHROP M. PHELPS, M.D., Director of the Children's Rehabilitation Institute, Inc., Baltimore. Pp. 158; illustrated. Springfield, Ill.: Charles C Thomas, 1939. Price, \$2.00.

STEVENSON'S tuberculosis, Ibsen's diabetes, Sternberg's periodic insanity, and Helen Keller's twofold afflictions did not prevent their rise to fame. Indeed, art has been said to be the offspring of poor health. The author was badly crippled at birth and is now fifty-eight years old. At the earnest solicitation of friends, she reveals her life in an autobiography of two parts, the first of which was written twenty years ago. It appears probable that at birth, intracranial injury caused hemorrhage into the basal nuclei, which brought about great, permanent, physical disability. From this resulted disabled locomotion, athetoid movements of the upper extremities, disturbance in the mechanism of breathing, and imperfect movements of tongue rendering oral speech impossible. Since a fall in early childhood, locomotion has been possible only through the use of an especially constructed tricycle. The frequent involuntary movements are so disabling as to permit of only one-finger typing, and verbal communication is through the medium of her shorthand manual sign language, somewhat similar to that of deaf mutes; conversation is accomplished by pointing to the letters of the alphabet attached to a piece of cloth. With such limited means of motor expression, these achievements compel admiration from all familiar with her. Many afflicted by severe physical handicaps will gain courage from reading the excellently written life by this mentally superior woman, who manifests neither self-pity nor craving for sympathy.

N. Y.

LIFE'S BEGINNING ON THE EARTH. By R. BEUTNER, M.D., PH.D., Professor of Pharmacology at the Hahnemann Medical College and Hospital of Philadelphia. Pp. 222; 80 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, \$3.00.

THE past few years have witnessed much literary popularization of the results of scientific investigation. The justification for the widespread dissemination of such knowledge is a debatable question, as even with accurate descriptions of experiments and careful interpretations of their meaning by the author, the layman, for whom such works are written, is in constant danger of obtaining erroneous conceptions because of his own

lack of critical judgment in such matters. Much as a great poem loses its meaning and force when put into the verbal and grammatical construction of every-day conversational speech, so do the implications of a scientific treatise become distorted when couched in other than scientific language. Such books are sold to the public upon the basis of their "startling revelations" and by their appeal to the mystical, the excitingly romantic attitudes which in a sober science do not exist.

In *Life's Beginning on Earth* the author attempts to convince his audience of the truth of his hypothesis by four "approaches": 1, The resemblances between vital growth and crystallization; 2, an interpretation of life as the outstanding property of the carbon atom; 3, the importance of salt and water for life; and 4, the animal considered as a machine.

As usual in such pseudoscientific literature, the author is not careful to distinguish emphatically between fact and theory. His whole-hearted acceptance of the viability of viruses, for example, differs with the attitudes of the very scientists whose work he adopts as evidence.

The book abounds in colorful descriptions such as: "On the hot and sultry earth, loaded with lifeless organic matter, violent thunderstorms raged; unspeakably brilliant and powerful lightnings played in the heavens, loosening frightful forces upon the carbon-containing gases of the atmosphere, bringing into existence numerous compounds of carbon. After millions of years self-regenerating enzymes were formed"; this is the essence of the author's hypothesis.

Life's Beginning on Earth is an entertainingly fanciful story which lacks in importance the wealth of its author's enthusiasm.

D. C.

CLINICAL LABORATORY METHODS AND DIAGNOSIS. A Textbook on Laboratory Procedures with Their Interpretation. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories and Gradwohl School of Laboratory Technique; Formerly Director of Laboratories, St. Louis County Hospital, etc. Pp. 1607; 492 text illustrations and 44 color plates. Second edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$12.50.

FOLLOWING his book on Laboratory Technique, published in 1933 (see Review, this JOURNAL, 184, 865, 1932), the author in 1935 brought out the first edition of this larger work. This second edition is still larger—in fact even somewhat cumbersome—with amplified sections and new illustrations. The chapter on hematology, for instance, has been increased by 100 pages, 11 pages of which are given to consideration of the unsettled problem of the origin of blood cells, and $7\frac{1}{2}$ more to the physiology of the hematopoietic organs. This seems unnecessary, even out of place, in a book of this kind. Similar inclusions of questionably wide scope add up to a considerable portion of an unwieldy book, with a corresponding effect on the price. On the other hand, the book certainly contains a wealth of information in readily available form.

E. K.

MEDICINE IN MODERN SOCIETY. By DAVID RIESMAN. Pp. 226. Princeton: Princeton University Press, 1938. Price, \$2.50.

THIS timely, important and interesting volume is an amplification of the author's recent Vanuxem lectures at Princeton. Without strain, it covers such superficially diverse subjects as the history of medicine—necessarily in very brief survey—cancer, the neuroses, and other aspects of modern and preventive medicine, and the recent developments of socialized medicine.

Yet all follow in logical sequence, combining to elucidate the basic topic of the modern doctor's relation to the patient and to society. The reader will eventually agree with the author's belief that "the history of medicine is in reality an epitome of the history of civilization and should form a part of every man's culture." Striking are the author's 28 items selected as peaks in medical history; of these discoveries only 8 were made more than a century ago, while 10 or more can properly be ascribed to the 20th century. Small wonder, then, that the old relation of doctor to patient has been disturbed and the best new relations not yet firmly established. It is indeed significant when such a wise physician, possessing an extensive knowledge of the history of his profession and of culture in general, strengthened by a long and active career in practical and in organized medicine, concludes that today's medical service to the public is capable of great improvement and that the organized profession has been backward in the movement to remedy the situation. The charm of the author's simple, homely, yet arrestingly illustrative style and the store of knowledge and wisdom exhibited can only be appreciated by reading the book itself. This procedure is highly recommended.

E. K.

NEW BOOKS.

Clinical Gastroenterology. By HORACE WENDELL SOPER, M.D., F.A.C.P., St. Louis, Mo. Pp. 314; 212 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$6.00.

Memorialia Herman Boerhaave 1738-1938. Optimi Medici. Pp. 133; 16 illustrations. Haarlem: De Erven F. Bohn N.V., 1939. Price, Hfl. 1.90.

The Vaginal Diaphragm. Its Fitting and Use in Contraceptive Technique. By LE MON CLARK, M.S., M.D., Chicago, Illinois. Pp. 107; 53 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$2.00.

Whence? Whither? Why? A New Philosophy Based on the Physical Sciences. By AUGUSTA GASKELL. Introduction by F. K. RICHTMYER, Professor of Physics, Cornell University; Dean of the Graduate School. Pp. 312. New York: G. P. Putnam's Sons, 1939. Price, \$2.50.

This book aims to answer such questions as: "Is there life after death? Is there a personal God who cares about man? Were we put on this earth for a definite purpose? And if so, what is that purpose? Or does Science discredit the belief in God and immortality? 'Crush the brain and that ends all'; is that true? Can we believe the Bible, in the face of the cold facts of Science?"

Synopsis of Pulmonary Tuberculosis. By JACOB SEGAL, M.D., Physician in Charge of Fordham Hospital Tuberculosis Clinic, New York; Associate Visiting Physician, Riverside Hospital, New York, and Bronx Hospital. Foreword by the Late POL N. CORYLLOS, M.D., F.A.C.S., Professor of Clinical Surgery, Cornell Medical College; Director of Thoracic Surgery at Seaview and Metropolitan Hospitals, New York, etc. Pp. 150; illustrated. New York: Oxford University Press, 1939. Price, \$2.75.

League of Nations. Bulletin of the Health Organisation, Vol. 7, Nos. 4 (Aug.) and 5 (Oct.), 1938. Pp.: No. 4, 73; No. 5, 217. New York: Columbia University Press, 1938. Price, 65c each.

No. 4 gives information concerning the activities of the Organisation. Among other items, the volume contains two reports of special interest. The first is by the Commission on Physical Education; the other deals with certain technical aspects of nutrition. No. 5 is specially devoted to the question of biological standardisation. It also contains studies on the international standard of vitamin B and the Report on the Third International Conference on the Standardisation of Hormones.

- Studies on the Size of the Red Blood Cells Especially in Some Anaemias.* By ERIK MOGENSEN. Pp. 216; 43 illustrations. Copenhagen: Ejnar Munksgaard, 1938; London: Oxford University Press, 1938.
- The Medical Clinics of North America*, Vol. 23, No. 2 (Baltimore Number—March, 1939). Pp. 294; illustrated. Philadelphia: W. B. Saunders Company, 1939.
- Ueber die Integrative Natur der Normalen Hornbildung.* Teil III. Systematischer Rückblick. By GOSTA EKEHORN, D:R MED., Stockholm. Pp. 292. Helsingfors: Printed by Mercators Tryckeri, 1938.
- Studies of Trauma and Carbohydrate Metabolism with Special Reference to the Existence of Traumatic Diabetes.* By VIGGO THOMSEN. Pp. 416; illustrated. Copenhagen: Ejnar Munksgaard, 1938. Price, d. Kr. 15.
- Chemie und Physiologie des Eiweisses* Mit Unterstützung der Stadt Frankfurt a.M. 3. Frankfurter Konferenz für Medizinisch-naturwissenschaftliche Zusammenarbeit am 2. und 3. Juni, 1938. Herausgegeben von DR. R. ORTO, Geh. Med.-Rat. Direktor des Staatl. Instituts für. exper. Therapie und des Forschungsinstituts für Chemotherapie, Honorarprofessor in der med. Fakultät, Frankfurt a.M., DR. K. FELIX, o. Professor für vegetative Physiologie, Frankfurt a.M., and DR. F. LAIBACH, o. Professor für Botanik, Frankfurt a.M. Pp. 203. Dresden: Theodor Steinkopff, 1938. Price, Paper, Rm. 6.75.
- Feminine Hygiene in Marriage.* By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by WINFIELD SCOTT PUGH, B.S., M.D. Pp. 155; illustrated. New York: Harvest House, 1938. Price, \$2.00.
- Problems of Ageing.* Biological and Medical Aspects. A Publication of The Josiah Macy, Jr., Foundation. Edited by E. V. COWDRY, Washington University, St. Louis. Twenty-six Contributors. Pp. 758; 120 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$10.00.
- An Introductory Guide to Biochemistry.* By SIDNEY BLISS, PH.D., Professor of Biochemistry, Tulane University School of Medicine. Pp. 103. Philadelphia: W. B. Saunders Company, 1939. Price, \$1.25.
- Superfluous Hair and Its Removal.* By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by M. H. MORTON, M.D. Pp. 155; illustrated. New York: Harvest House, 1938. Price, \$2.00.
- You Can't Eat That!* A Manual and Recipe Book for Those Who Suffer Either Acutely or Mildly (and perhaps unconsciously) from Food Allergy. By HELEN MORGAN. Foreword by Dr. WALTER C. ALVAREZ, of the Mayo Clinic. Pp. 330. New York: Harcourt, Brace & Co., 1939. Price, \$2.50.
- Malaria in Panama.* (The American Journal of Hygiene, Monographic Series, No. 13, January, 1939.) Supported by the De Lamar Fund of The Johns Hopkins University. By JAMES STEVENS SIMMONS, B.S., M.D., PH.D., S.D., Lt. Col., Medical Corps, U. S. Army, etc. With the Collaboration of George R. CALLENDER, M.D., Lt. Col., Medical Corps, U. S. Army, etc., DALFERES P. CURRY, M.D., Major, Medical Reserve Corps, U. S. Army, etc., SEYMOUR C. SCHWARTZ, B.S., M.D., Dr. P.H., Lt. Col., Medical Corps, U. S. Army, etc., and RAYMOND RANDALL, D.V.M., Lt. Col., Veterinary Corps, U. S. Army, etc. Pp. 326; 32 figures and 58 tables. Baltimore: The Johns Hopkins Press, 1939. Price, \$1.10.
- The Principles and Practice of Ophthalmic Surgery.* By EDMUND B. SPAETH, M.D., Associate Professor of Ophthalmology in the Graduate School of Medicine at the University of Pennsylvania; Ophthalmologist to the Orthopedic Hospital and Infirmary for Nervous Diseases, Philadelphia; Consultant in Ophthalmology to the Philadelphia Hospital for the Insane (Byberry), etc. Pp. 835; 413 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$10.00.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF
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ADRENAL CORTICAL HORMONE THERAPY.*

NINE years have elapsed since patients with Addison's disease were first treated with potent extracts of adrenal cortex (Rowntree and Greene,⁶⁸ and Hartman, Aaron and Culp³³), prepared independently by Swingle and Pfiffner,⁷⁴ and Hartman and Brownell.²⁹ During the 4 years subsequent to this discovery, difficulties encountered in the preparation of large quantities of potent extract and in the standardization of the hormone limited clinical trial. However, numerous reports regarding studies in experimental adrenal insufficiency and patients with Addison's disease, treated with adrenal cortical extract, appeared during this period. The beneficial effect of sodium salts (Loeb,⁵⁰ and Harrop, Weinstein *et al.*,²⁷ and the detrimental effect of potassium (Truszkowski and Zwemer,⁸⁷ and Wilder, Kendall *et al.*⁹²) in adrenal insufficiency were not fully appreciated by most investigators at this time. Thus, in many instances, it is difficult to evaluate the benefits ascribed to hormone therapy when data regarding the mineral intake are not given.

Approximately 5 years ago, adequate quantities of adrenal cortical hormone became available commercially. Since that time nearly every known human disease has been treated with adrenal cortical extract. In a great many instances, the effect of treatment in a single patient has been reported; in other studies, the quantity of material administered was obviously inadequate. From a great number of clinical observations and experiments, there emerge a few conditions in which it appears that adrenal cortical hormone therapy is of benefit.

Recently, Steiger and Reichstein⁷³ announced the preparation of desoxy-corticosterone acetate from stigmasterol, and subsequently Reichstein and von Euw⁶⁶ recovered desoxy-corticosterone from an extract of adrenal cortex. It has been shown (Thorn and Eisenberg⁸¹) that daily intramuscular injections of this compound will maintain adrenal-

* For previous reviews on this subject the reader is referred to Greene,¹⁶ Grollman¹⁹ and Loeb.²¹

ectomized dogs in excellent condition, despite a diet low in sodium and chloride. The availability in the near future of crystalline preparations of adrenal cortical hormone, synthetically prepared, stimulates a review of the possible applications of adrenal cortical hormone therapy at this time.

Methods of Administering Adrenal Cortical Hormone. 1. *Oral Therapy.* Adrenal cortical extract, in aqueous or saline solution, is largely destroyed during its passage through the intestinal tract (Hartman, Thorn, Durant³⁷). Two methods have been adopted for preserving the activity of orally administered hormone: 1, adsorption on charcoal (Grollman, Firor and Grollman²¹); and 2, preservation with glycerol (Hartman and Pohle³⁰). The requirement of hormone administered orally in adrenalectomized dogs or patients with Addison's disease, is at least 3 times that required by subcutaneous injection (Thorn, Emerson, Eisenberg⁸²).

2. *Subcutaneous, Intramuscular and Intravenous Therapy.* Commercial extracts of adrenal cortex are prepared in a solution of normal saline or dilute alcohol for subcutaneous injection. The preparations are relatively pure, containing 0.5 to 3 mg. of solids per cubic centimeter. For immediate action, these extracts may be injected intravenously. However, the duration of action following intravenous injection is transient (Harrop and Thorn²⁵). It is also possible that a resistance to further action of the hormone may arise following intravenous administration (Hartman, Lewis and McConnell³⁶).

A crystalline preparation of adrenal cortical hormone, desoxy-corticosterone, has been prepared in a solution of oil for intramuscular injection (Miescher, Fischer and Tschopp⁵⁹). Under local anesthesia, pellets, composed of crystals of desoxy-corticosterone acetate, may be implanted subcutaneously (Thorn, Howard *et al.*⁸⁴).

Standardization of Hormone. Maintenance of adrenalectomized animals appears to be the only reliable test for determining the presence of adrenal cortical hormone in a given preparation. Until crystalline preparations have been proved to be completely supplementary, an absolute standard of biological activity is not practical. For purposes of comparative assay, numerous methods of standardization have been proposed. In general, these are concerned with (a) maintenance of normal growth curve of young rats (Hartman and Thorn,³² Grollman and Firor^{20a}), (b) maintenance of adrenalectomized dogs (Harrop, Pffner, *et al.*²⁶) and cats (Hartman and Pohle³⁰). In both of these methods the determination of changes in the non-protein nitrogen content of the blood is important; (c) tests of muscular efficiency in adrenalectomized animals (Everse, de Fremery,¹² and Ingle⁴³) and (d) tests based upon the increased susceptibility of adrenalectomized animals to drugs, toxins and physical agents (Perla and Gottesman,⁶² and Selye and Schenker⁷¹). Conditions in which the use of adrenal cortical hormone therapy appears to be beneficial follow:

Addison's Disease. Typical signs and symptoms of Addison's disease rarely are manifest until extensive destruction of functioning adrenal cortical tissue has occurred (Guttman²³). Thus patients with severe Addison's disease may require almost complete replacement therapy. In all patients with Addison's disease the response to cortical hormone therapy may be modified by several factors (a) the type of pathologic

lesion responsible for the adrenal cortical deficiency (Snell⁷²), (b) the presence of extensive medullary destruction (Harrop²⁴) and (c) the possibility of permanent changes occurring in other organs as the result of prolonged adrenal insufficiency (Grollman and Firor^{20b}).

Early reports (Rowntree, Greene *et al.*,⁶⁹ Hartman, Bowen *et al.*,³⁵ Baird and Albright,² and Harrop, Weinstein *et al.*²⁷) regarding the use of adrenal cortical extracts in the treatment of Addison's disease were encouraging, and in selected cases very striking. However, in a review of 46 patients treated with adrenal cortical hormone at the Mayo Clinic between 1930 and 1933, Snell⁷² noted that the expected length of life was only slightly prolonged although marked and continued improvement was observed in some patients. It is apparent that the failure to improve the average life expectancy of these patients was due in large measure to inadequate treatment resulting from the limited supply of cortical hormone. The low potency of some of the extracts, their prohibitive cost and, in addition, the little recognized need for frequent subcutaneous injections of hormone throughout the day, account for many of the disappointing results with hormone therapy in the treatment of Addison's disease.

During this same period, the strikingly beneficial effect of sodium salts in the treatment of Addison's disease was described by Loeb,⁵⁰ and Harrop *et al.*,²⁷ and as a result, some doubt was expressed as to the value, if any, of adrenal cortical extract therapy in the treatment of Addison's disease. It was evident that patients could be kept alive, and in some cases could be maintained in fairly good condition by means of treatment with large quantities of sodium salts alone. It was also evident that the daily requirement of hormone could be greatly reduced by the addition of sodium salts to the diet of both patients with Addison's disease and animals with experimental adrenal insufficiency. In many patients, however, treatment with added sodium salts and a diet of low potassium content (Wilder *et al.*⁹²) was not sufficient for maintenance and, in addition, daily injections of hormone were required (Greene¹⁶). It is obviously difficult to evaluate the benefits of hormone therapy in patients maintained on a regimen of high sodium and chloride intake combined with small doses of extract.

In 1936 it was shown that adequate quantities of adrenal cortical extract (12 to 30 cat units daily, injected subcutaneously in divided doses), *without supplementary sodium chloride therapy* or reduction in the potassium content of the diet, resulted in a positive sodium and chloride balance, a negative potassium balance, an increase in plasma volume and total plasma content of sodium and chloride, an increase in blood pressure, weight gain, improved appetite and muscular strength (Thorn, Garbutt *et al.*^{85b}). Withdrawal of extract treatment promptly resulted in a diuresis associated with an increased renal loss of sodium and chloride decreased renal loss of potassium, reduction in plasma volume and total plasma content of sodium and chloride, reduction in blood pressure, loss of weight and decreased appetite and strength. Restoration of treatment with adrenal cortical extract, alone, caused the disappearance of these signs and symptoms and resulted in a return toward normal. Furthermore, repeated intravenous injections of adrenal cortical extract were found to have an immediate effect on the renal excretion of sodium and potassium in patients with Addison's disease

(Thorn, Garbutt *et al.*^{85c}). Thompson, Thompson *et al.*⁷⁹ were able to maintain 4 patients with Addison's disease, in good condition, for long periods of time, by means of daily injections of 10 to 20 cc. of a potent commercial adrenal cortical extract (this quantity of extract being derived for 750 to 1500 gm. of beef adrenal). No added sodium chloride therapy or reduction in diet content of potassium was used. It appears from these studies that adequate hormone therapy can result in restoration of patients with Addison's disease to normal activity without regard to the mineral intake. However, the cost of this type of treatment and the necessity for frequent subcutaneous injections limit both its applicability and desirability.

Oral administration of adrenal cortical extract is efficacious in the treatment of animals with experimental adrenal insufficiency (Britton, Flippin, and Silvette,⁵ Grollman and Firor,^{20a} Hartman and Pohle³⁰), and in the treatment of patients with Addison's disease (Thorn, Emerson and Eisenberg⁸²). For patients with Addison's disease the requirement of orally administered hormone, in either glycerol solution or as a charcoal adsorbate, is at least 3 times the quantity of hormone necessary when injected subcutaneously in aqueous solution. Effective oral treatment for most patients with severe Addison's disease is impractical at present because of the cost.

Crystalline compounds, corticosterone and dehydro-corticosterone isolated by Mason, Meyers and Kendall,⁵⁵ and de Fremery, Laquer *et al.*¹⁴ from extracts of the adrenal cortex, have been reported to maintain adrenalectomized animals in good condition. These compounds have not been available for clinical trial. The desirability of employing crystalline preparations of known chemical composition in the treatment of Addison's disease is evident. In 1937, Steiger and Reichstein⁷³ announced the preparation of desoxy-corticosterone acetate from stigmasterol, and recently Reichstein and von Euw⁶⁶ succeeded in isolating desoxy-corticosterone from an extract of adrenal cortex, thus establishing the natural occurrence of this compound. The synthetically prepared compound was shown to be capable, on injection, of maintaining adrenalectomized dogs in good condition, despite a diet low in sodium and chloride (Thorn, Engel and Eisenberg,^{83a} Thorn and Eisenberg⁸¹). Studies on 8 patients with Addison's disease treated with daily intramuscular injections of desoxy-corticosterone acetate in sesame oil (Thorn, Howard and Emerson⁸⁶), indicate that treatment with this compound (5 to 25 mg. daily) resulted, in all of the patients, in sodium and chloride retention, increased potassium excretion, increased plasma volume and total plasma content of sodium and chloride, an increase in body weight and blood pressure, improved appetite and strength. These changes occurred without supplementary treatment with sodium salts or decreased potassium content of the diet. Withdrawal of desoxy-corticosterone acetate treatment resulted in a diuresis, loss of sodium and chloride, decreased excretion of potassium, decrease in plasma volume with hemoconcentration and a decrease in total plasma content of sodium and chloride, loss in weight and decrease in appetite and strength. Institution of treatment with desoxy-corticosterone acetate, following a period of withdrawal resulted again in all of the changes previously observed. As far as could be determined, the treatment with desoxy-corticosterone acetate resembled in every way the effect of treatment

with potent adrenal cortical extract. It appeared from these studies that 1 mg. of desoxy-corticosterone acetate, in oil, injected once daily intramuscularly, was equivalent to approximately 3 cc. of a potent commercial adrenal cortical extract injected subcutaneously, the latter being administered in divided doses. Levy-Simpson,⁴⁸ noted that desoxy-corticosterone acetate treatment was qualitatively similar to that of adrenal cortical extract treatment in 2 patients with Addison's disease.

Applying the technique which Deanesly and Parkes⁹ employed in experimental studies on sex hormone administration, Thorn, Engel and Eisenberg^{83b} recently demonstrated that the subcutaneous implantation of pellets of crystalline desoxy-corticosterone acetate is a practical and very economical method of administering this hormone to adrenalectomized dogs. Following the implantation of pellets of desoxy-corticosterone acetate, the animals were maintained in excellent condition for long periods, despite a diet low in sodium and chloride. Preliminary experiments in which this technique was applied clinically indicate results equally as successful as those observed in experimental animals (Thorn, Howard *et al.*⁸⁴). Such a form of treatment provides for a continuous supply of hormone and the studies demonstrated a considerable saving of hormone. If this form of therapy proves to be practical, patients with Addison's disease could be treated effectively by this method at moderate cost.

Although striking changes in the clinical condition of patients have followed continued treatment with either potent adrenal cortical extract or synthetically prepared desoxy-corticosterone acetate, changes in the pigmentation of patients with Addison's disease has been neither uniform nor predictable (Greene,¹⁶ Hartman *et al.*,³⁸ Thorn *et al.*⁸⁶). It is possible that intensive hormone therapy has not been continued long enough, since, for practical purposes, most patients are maintained on large doses of sodium salts and relatively small quantities of hormone. It is also possible that the preparations which have been used may not contain the factor which influences pigmentation, even though these preparations do possess life-maintaining property. It has also been suggested that changes in pigmentation may be related to disturbances in function of the medulla (Harrop²⁴). However, pathologic data provide conflicting evidence on this point (Greenhow,¹⁸ Barker³). Szent-Gyorgyi⁷⁶ has suggested the use of ascorbic acid in conjunction with adrenal cortical extract therapy in the treatment of pigmentation in patients with Addison's disease. Szule⁷⁷ has reported favorably on this method of treatment. In the author's experience (unpublished data) ascorbic acid administered by mouth or parenterally has been ineffective in significantly altering the pigmentation of patients with Addison's disease.

It has been shown by Kendall *et al.*⁴⁶ that disturbances in the concentration and distribution of sodium and potassium in the body result in altered carbohydrate metabolism. However, even at a time when electrolyte concentration and distribution is apparently normal, patients may, on occasion, develop hypoglycemia. It cannot be stated at this time whether a persistence in the disturbance of carbohydrate metabolism indicates (a) lack of intensive hormone therapy (b) an absence of a necessary factor in the preparations now employed or (c) a manifestation

of a disturbance in adrenal medullary function. The observations of Lukens and Dohan,⁵³ and of Long, Fry and Thompson⁵² render the second of these three possibilities unlikely. For practical purposes, it seems advisable at present, to maintain all patients with Addison's disease on a diet high in readily available carbohydrate.

The success of treatment in Addison's disease depends in part upon the etiologic factor responsible for the changes in the adrenals, and to a large measure upon the patient's ability to follow prescribed treatment. Successful treatment should permit the patient to resume his normal occupation. Maintenance of life alone should not be considered sufficient. In some patients, the only treatment necessary is added sodium chloride or a combination of sodium salts; others may need restriction of potassium intake in addition to added sodium chloride therapy; most patients, in order to resume normal activity, will require hormone therapy. Patients receiving hormone therapy, rarely need to suffer the inconvenience imposed by adhering to a diet, low in potassium; added sodium chloride therapy will greatly reduce the hormone requirement. It has not been demonstrated conclusively that full replacement with hormone therapy offers advantages over combined hormone and mineral therapy. The high cost of hormone preparations will prevent most patients from being treated with hormone alone. Hormone may be given orally, but in severe Addison's disease, since this method requires at least three times the quantity of extract necessary by subcutaneous injection, it is usually too costly. Administration of extract in divided doses is much more efficacious than a single daily injection. Intravenous injections of extract, exert only a transient effect and may result after repeated injections, in the formation of substances antagonistic to the hormone action (Hartman *et al.*³⁶). These changes do not occur following the subcutaneous injection of adrenal cortical extract (Harrop and Thorn²⁵). For this reason, intravenous administration of extract should be reserved for emergency treatment.

Surgical Operations on Patients with Addison's Disease. By using large doses of adrenal cortical extract, 40 cc. daily, in divided doses for 2 days preoperatively, 20 cc. of extract immediately after operation, and 10 cc. twice daily subsequently, in addition to intravenous sodium chloride, Greene, Walters and Rowntree¹⁷ were able to perform successfully an epididymectomy and orchidectomy for tuberculosis in a patient with Addison's disease. The great improvement which follows intensive therapy in patients with Addison's disease, justifies the consideration of the surgical removal of a focus of tuberculosis. This encouraging report indicates the possibility of performing such operations successfully in patients with Addison's disease.

Acute Adrenal Insufficiency. A. *Associated with surgical procedures involving the adrenal gland.* Exploration or denervation of the adrenals, resection of adrenal tissue for hypertension, and removal of adrenal tumors may result in symptoms of acute adrenal insufficiency, either as a result of tissue removed, or as a consequence of hemorrhage into the gland. Intensive therapy (intravenous saline and glucose, and large quantities of adrenal cortical extract 50 to 150 cc. daily, injected intravenously and subcutaneously) may be required in order to effect recovery (Walters and Kepler,³⁸ and Prather⁶⁴).

B. *Bilateral adrenal hemorrhage* with death in 24 to 48 hours has been reported in 1% of autopsies on new-born infants (Levinson⁴⁷). In a series of 8 cases, 6 were noted to have had breech delivery and 2 followed Cesarean section. In the latter, rather vigorous slapping over the lumbar region had been used in attempting resuscitation. As yet, no instance of treatment in this disorder has been reported. If the diagnosis were suspected, immediate institution of intensive treatment would seem to be indicated.

C. *Waterhouse-Friderichsen Syndrome*. The occurrence of extensive hemorrhage in the adrenals during the course of meningococcemia, scarlet fever, diphtheria, pneumonia and poliomyelitis is well known (Aegerter¹). In many patients with this complication the infection may be adequately controlled by chemical or serum therapy and the life of the patient then depends upon the successful treatment of acute adrenal insufficiency. Bilateral adrenal hemorrhage, frequently complicates the fatal termination of acute pemphigus. Recently, Talbott⁷⁸ has treated 5 patients suffering from acute pemphigus by means of 10 to 15 cc. daily of adrenal cortical extract, administered subcutaneously in divided doses, and 1500 cc. of normal saline intravenously daily. A satisfactory remission occurred in each case. Normal saline solution, alone, was not sufficient. Five control cases died within 5 weeks after admission to the hospital. Two of these patients were examined post-mortem and found to have bilateral adrenal hemorrhages. Obviously, adrenal insufficiency is not the etiologic factor in acute pemphigus, but this report indicates the possibility of treating the acute bilateral adrenal hemorrhage which not infrequently complicates this condition. Hormone treatment of the Waterhouse-Friderichsen syndrome in infections which are readily amenable to serum or chemotherapy would seem to provide a promising possibility of therapeutic response.

Diagnosis of Adrenal Insufficiency. The desirability of undertaking treatment early in the course of adrenal insufficiency is readily understood. However, the difficulty of establishing a diagnosis of adrenal insufficiency in patients who do not present all of the classical signs and symptoms of Addison's disease is well known. Three types of procedures have been suggested as an aid in the diagnosis of adrenal insufficiency: 1, the precipitation of the signs and symptoms of adrenal insufficiency following a period of sodium chloride withdrawal (Harrop *et al.*²⁷); 2, the estimation of the concentration of sodium and chloride in the urine, under standard conditions (Cutler, Power and Wilder⁸); and 3 the effect of adrenal cortical hormone on the renal excretion of electrolytes (Thorn, Garbutt *et al.*^{85b}). It is apparent that no one of these tests is infallible. The first procedure is relatively simple, but may end disastrously (Lillienthal⁴⁹). The second involves a relatively simple metabolic study and necessitates only the determination of urinary chloride. Again, however, this test may result in the precipitation of signs of acute adrenal insufficiency. The third procedure is safe, but involves careful balance studies conducted in a metabolism unit and hence is not generally applicable.

Gordon, Sevringhaus and Stark¹⁵ have studied the effect of adrenal cortical hormone therapy on the blood pressure and symptomatic response of 32 patients who complained of asthenia, as the presenting symptom. Seventeen of these patients were definitely benefited by

hormone administration, and subsequently have been maintained on sodium salts of adrenal cortical extract with marked benefit. It was thought by these authors that the symptoms and hypotension of the group responding to hormone therapy indicated adrenal insufficiency.

Post Infectious Asthenia. Changes in the adrenals (focal necroses and hemorrhages, cloudy swelling and congestion) are known to occur during the course of acute infections (MacKenzie,⁵⁴ Cowie and Beaven⁶). It is possible that in some patients, the marked prostration and hypotension which persist after the subsidence of infection may, in part, be due to adrenal insufficiency. Robbins⁶⁷ has reported the successful treatment of post-infectious asthenia following acute streptococcic infections. Hartman, Beck and Thorn³⁴ have reported improvement (as measured by the ergometer) in post-infectious asthenia. The latter authors point out the difficulty of obtaining suitable control periods. It appears probable that adrenal cortical hormone therapy, or sodium salts, or a combination of both forms of treatment may be efficacious in alleviating post-infectious asthenia in selected cases. However, the difficulty in obtaining critical data regarding the efficacy of any form of therapy in this syndrome is apparent.

Circulatory Shock. The presence of anhydremia and shock in the crisis of adrenal insufficiency has suggested the possibility of using adrenal cortical hormone in the prevention or treatment of shock initiated by other causes. Swingle, Parkins *et al.*⁷⁵ have demonstrated the value of adrenal cortical hormone therapy in protecting adrenalectomized dogs from the shock which follows intestinal manipulation. Heuer and Andrus³⁹ have shown that 10 to 40 cc. of a commercial adrenal cortical extract protected normal dogs from the shock induced by injecting aqueous extracts of closed intestinal loops. Treated animals lost 8.5% of their plasma volume whereas untreated animals lost 30.5%. Epinephrin, cholesterin or vitamin C were ineffective. Treatment with adrenal cortical extract was given either prior to, or simultaneously with the injection of the noxious agent. Attempts to restore shocked animals, by means of adrenal cortical extract were ineffective. Restoration by means of transfusion or a combination of cortical hormone and transfusion was successful. Greene¹⁶ notes the favorable effect of adrenal cortical hormone therapy in a patient in shock following partial intestinal obstruction with vomiting and dehydration. MacLean, Sullivan and Zwemer⁵⁵ have reported a satisfactory therapeutic response following the use of adrenal cortical extract in the treatment of children with acute gastro-enteritis. In a series of 50 patients treated with injections of adrenal cortical extract (1 to 2 cc. every 4 to 12 hours) preoperatively and postoperatively, Reed has reported maintenance of blood electrolytes, stabilization of blood pressure and rapid healing of incisions. It seems unlikely that such small quantities of extract could have any appreciable effect.

Etherization of normal dogs results in a reduction in plasma volume of approximately 12% (McAllister⁵⁷). This fluid shift may be prevented by repeated intravenous injections of adrenal cortical extract prior to and during the administration of ether (McAllister and Thorn⁵⁸). Dragstedt, Mills and Mead¹⁰ noted that adrenal cortical extract treatment in experimental animals greatly ameliorated the symptoms of

anaphylactic shock without reducing the incidence. Again in these experiments, the adrenal cortical extract was given prior to the shocking dose of serum.

Severe burns in experimental animals have been treated by means of adrenal cortical extract (Einhauser¹¹). Although this author reports an increase in the survival period of animals treated with adrenal cortical extract ($\frac{1}{3}$ cc. of extract, per animal, per day), it seems unlikely that this small quantity of material would have any significant effect. Wilson, Rowley and Gray⁹³ using 1 to 2 cc., hourly, of commercial adrenal cortical extract report the beneficial effect of this treatment in 3 infants with intensive burns. They state that suprarenal cortical hormone should be used only as adjuvant treatment. Hartman²⁸ has reported the beneficial effect of large doses of adrenal cortical extract in the treatment of shock occurring in an infant following severe burns. It is difficult to determine the benefit derived from adrenal cortical extract treatment in patients with severe burns because of the inability to study suitable control cases and because of the desirability of including the supportive measures generally indicated. Animal experiments would suggest that adrenal cortical hormone therapy might be expected to reduce the incidence or intensity of shock if such therapy were administered prior to the shocking procedure. The beneficial effect of adrenal cortical hormone therapy in the prevention of shock in experimental animals is due, in part at least, to the preservation of plasma volume. There is little evidence, except in *adrenalectomized animals*, to show that adrenal cortical hormone therapy is of any benefit when given after the symptoms of shock have appeared.

Acute Infections. Adrenal cortical hormone therapy increases the resistance of *adrenalectomized animals* to infection (Hartman and Scott³¹). This is considered to be largely related to the general improvement in the condition of the animals. However, Wenner and Cone⁹¹ have reported that the opsonic power of serum of both suprarenalectomized and normal animals is increased by injections of cortical extract. Furthermore, Wenner⁹⁰ reported marked success in the treatment of experimental maxillary sinusitis with adrenal cortical extracts. Scott, Bradford *et al.*⁷⁰ have shown that adrenal cortical extract treatment was of *no benefit* in (a) protecting normal guinea pigs from the effect of diphtheria toxin (b) protecting normal rats from trypanosome infection or (c) protecting normal mice from pneumococcus infection. Although the quantity of extract used in these studies was small ($\frac{1}{2}$ the maintenance dose for adrenalectomized guinea pigs being injected daily in the infected animals), this dose of hormone corresponds closely to that which has been used in clinical studies (Najib-Farah⁶¹). Thus far, with the doses employed, no data have been presented which conclusively demonstrate the effectiveness of adrenal cortical hormone in the treatment of acute infections in the human being.

Disturbances in Muscle Metabolism and Thyroid Function. Adrenal cortical extract therapy has been tried in muscular atrophy, muscular dystrophy and myasthenia gravis (Hartman, Beck and Thorn,³⁴ Greene,¹⁶ Bernhardt and Levy-Simpson⁴). Apart from a slight temporary improvement in some patients, the course of the disease has been unaffected by this form of therapy. Weinstein and Marlow⁹⁹ failed to observe any

beneficial effect of adrenal cortical extract, injected daily, in 17 patients with hyperthyroidism and in 2 patients with hypothyroidism. The dosage used was 9.5 cc. per day per patient (average) which represented 285 gm. of suprarenal cortex. Furthermore, no beneficial effect was observed in 3 patients with hyperthyroidism who were fed 18.6 gm. per day of raw suprarenal cortex.

Miscellaneous Conditions. Hoskins and Freeman^{42a} report that 1 gm. three times daily, of a glycerinated adrenal cortical extract, resulted after 3 weeks of treatment in an average weight gain of 3 kg. in 17 schizophrenic patients. The weight of 17 control normal subjects was unaffected by this treatment. Studies of this extract indicate that "cortin" is probably not the factor in the extract responsible for the change (Hoskins and Gottlieb^{42b}).

As stated earlier in this review, adrenal cortical extract therapy has been tried in a wide variety of clinical conditions, *i. e.*, vomiting of pregnancy (Kemp^{45a}), asthma (Fineman,¹³ Pottenger⁶³), psoriasis (Gruneberg²²) and glaucoma (Josephson⁴⁴). Varying degrees of success are reported in these conditions following adrenal cortical extract therapy. However, the data presented usually do not permit critical evaluation of the benefits ascribed.

Effect in Normal Human Subjects. Repeated intravenous injections of adrenal cortical extract (20 cat units hourly, for 4 hours) in normal human subjects resulted in an immediate effect on the renal excretion of electrolytes (Thorn, Garbutt *et al.*^{85a}). A marked decrease in the renal excretion of sodium and chloride, and an increased excretion of potassium were noted. Subsequently, it was shown that repeated intravenous injections of adrenal cortical hormone, throughout the day, resulted in a similar change in the 24-hour renal excretion of electrolytes (Thorn⁸⁰). Similar effects have been observed in normal dogs following the intravenous or subcutaneous injection of large quantities of adrenal cortical extract (Harrop and Thorn²⁵) and following the subcutaneous injection of 1 to 5 mg. of crystalline desoxy-corticosterone acetate in oil (Thorn, Engel and Eisenberg⁸³).

Hitchcock and Thorn⁴⁰ noted that injections of adrenal cortical extract in normal subjects resulted in a pronounced drop in oxygen consumed in maintaining the erect posture. Hitchcock, Grubbs and Hartman⁴¹ have confirmed this observation, and, in addition, have noted that a marked depression occurred in the oxygen consumption of subjects walking on a treadmill at the rate of 100 meters per minute. Missuro, Dill and Edwards⁶⁰ noted that the efficiency with which easy walking was performed was increased for some days after injections of adrenal cortical extract.

Summary and Conclusions. Adrenal cortical hormone is of definite value in the treatment of Addison's disease and conditions associated with acute adrenal insufficiency. The response to adrenal cortical therapy may be an aid in the diagnosis of adrenal insufficiency. It is possible that adrenal cortical hormone therapy may be of benefit in other disorders, but, to date, conclusive evidence has not been presented to substantiate this suggestion. Injections of adrenal cortical hormone have been shown to have a definite effect in normal human subjects.

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RADIOLOGY

UNDER THE CHARGE OF
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ROENTGENOLOGY IN THORACIC LESIONS.

"DURING the development of any particular branch of medical science there are, of necessity, periods of experimentation in which various angles of the problems encountered are explored. Eventually the time is reached when it becomes advisable to compile all the essential data that have accumulated and to integrate the essential facts into a satisfactory and workable scheme." With this introduction, Pesquera and Sampson⁹ suggest that there is, perhaps, nothing of greater importance in the field of thoracic roentgenography at this time than acceptance of a standardized technique that will make available, for the profession at large, comparable thoracic roentgenograms. Tracing the history of roentgenography of the thoracic cage from the discovery of the Roentgen rays, some 40 years ago, these authors present briefly the steps leading up to the present-day concept of a good thoracic roentgenogram. Such a concept, they point out, should represent the result obtained after the

proper manipulation of voltage, milliamperage, time of exposure, focal distances and the focal spot. The individual characteristic and the cause and the effect of each of these factors must be understood.

Their experience has been practical, and whatever conclusions they have drawn are based on the study of roentgenograms. In their studies they paid particular attention to the following points: (1) time of exposure; (2) penetration (contrast); (3) target-to-film distance; and (4) definition of shadows. They found that a satisfactory roentgenogram could be made with a $\frac{1}{10}$ to $\frac{1}{20}$ second exposure. In the roentgenogram, penetration is revealed by the relative value of the blacks and the whites and half-tones. It is by means of the relative values of the shadow that the physician determines the activity of a given pathologic process. The merging of the shadow with the surrounding normal tissue may be gradual or abrupt, and students of the roentgenogram feel reasonably secure in drawing conclusions therefrom, one way or the other. The differentiation of caseous and exudative lesions, in the presence of tuberculosis, from those of the proliferative and fibrous type is a matter of shadow-contrast evaluation. It is conceivable that if improper technique produced greater contrast, the physician might be misled in his deductions. It was a common occurrence, in the experience of Pesquera and Sampson, to have a roentgenogram which exhibited too much contrast suggest a reactivation of a focus, whereas a film of the proper shadow values would not convey this impression. On the basis of differentiation of tissue densities only, it would seem that the use of a grid for thoracic roentgenography should have an advantage; but there are equally important factors which render the use of a grid unsatisfactory. For example, stereoroentgenograms cannot be made with facility; also the occurrence of objectionable grid marks is likely to mar the daily output.

As target-to-film distances increase, undesirable enlargement becomes progressively diminished; according to Wilsey,¹¹ "Most of the decrease in enlargement has occurred within the four foot distance, beyond this the enlargement diminishes very slowly." On the other hand, as the distance increases, the area of the focal spot also must increase in proportion to the square of the focal film distance which, in itself, tends to nullify any gain in sharpness from long distances unless the efficiency of the focal spot (current-carrying capacity) is increased by greater anode slope, by anode rotation or by both.

Pesquera and Sampson credit Files⁴ with concisely summing up the definition by his stating that the best diagnostic results can be obtained only when a tube is used which has the smallest possible focal spot consistent with the part to be roentgenographed. Hence, the physician can confidently rely on small focus tubes (preferably rotary targets), moderate kilovoltages, 5 to 7 foot distances, and $\frac{1}{10}$ to $\frac{1}{20}$ of a second exposure times for the finest of stereoroentgenograms.

The relative cost of equipment necessary to produce relative gains in definition (sharpness of shadows) is presented by the previously mentioned authors in graphic form. They feel that it is now possible for the roentgenologist to obtain a roentgenogram which will enable him to make the diagnosis of early pulmonary tuberculosis and to follow the progress of his patient intelligently during the life of the patient. They believe that a standard diagnostic thoracic roentgenogram can

be made an accomplished fact and that it can efface Sir William Osler's statement: "More than any others, *some* roentgenologists need the salutary lessons of the dead house to correct their visionary interpretations of shadows."⁸

In the Hickey Lecture of 1938, Holmes,⁶ speaking of hemoptysis and its roentgenologic diagnosis, said: "No doubt the frequency with which this symptom appears as a presenting symptom varies widely in different clinics and with different physicians." His own experience agreed with that of Dr. Richard Cabot, who once said that from his observations at the Massachusetts General Hospital, the most common cause of blood-spitting was cardiac disease. To cardiac disease, Holmes would add valvular disease, pulmonary emboli and allied conditions. In general practice, he observed, tuberculosis still ranked among the first as a cause. The speaker had been particularly interested in a small group of cases of tuberculous origin in which the results of physical and roentgenologic examinations had been essentially negative, although the patients classed in this group may have had as a presenting symptom considerable pulmonary hemorrhage. In some instances, tubercle bacilli were found in the sputum. While it was difficult to prove beyond a doubt the actual source of the disease in this type of case, Holmes was convinced that a considerable percentage of the cases arose from ulcerations in the bronchi. In the cases of some patients, at least, calcified glands were demonstrated or bronchoscopic examinations revealed a definite erosion. The "lung stones" more familiar to older physicians were undoubtedly the calcified masses of glands which had ulcerated through into a bronchus, and were then expectorated. Such an accident was usually followed by blood-spitting, possibly by severe hemorrhage, and occasionally by the appearance of tubercle bacilli in the sputum.

Next to cardiac disease and bronchiectasis, perhaps the most common causes of blood-spitting, in Holmes' experience, have been the various tumors and ulcerations of the bronchi. He believes that primary tumors of the bronchi, either benign or malignant, are more often seen in general hospitals today than they were a few years ago. Whether this is due to an actual increase in the frequency of the disease or to an improvement in diagnostic methods is debatable. With the rapid advances being made in surgery of the thorax, Holmes said, it is becoming increasingly important, not only to make an accurate diagnosis, but to locate the lesion in a specific bronchus, to determine whether or not the lesion was single or multiple, and, in the occurrence of a malignant lesion, to determine whether it has extended to the regional gland. Much of this information required by the surgeon before advising or attempting operation, is supplied by roentgenologic and bronchoscopic examination. Lobectomy, Holmes believes, is now the therapeutic measure of choice, not only for tumors of the bronchi, but also for many cases of bronchiectasis.

The roentgenologic examination should include a roentgenoscopic study, to observe the movements of the diaphragm, the pulsations of the heart and great blood-vessels, the posterior mediastinum, any pathologic process present, and the changing of the lung shadows with different phases of the respiratory cycle. Most important of all, the proper roentgenographic procedure to be carried out to obtain data for accurate diagnosis will be determined. Roentgenograms taken at full inspiration,

Holmes emphasizes, often fail to show localized air trapping, or small regions of pneumothorax, which are easily demonstrated in roentgenograms taken at expiration. A process located below the diaphragm may be missed completely, even in stereoscopic roentgenograms, or a tumor situated close to the midline may appear as a mass of the hilar gland. Broad thin portions which lie with their long diameter in the anterior plane may be invisible in the anteroposterior view, especially if the roentgenograms are taken at a short target-to-film distance. These conditions are all much better demonstrated in a lateral view. The space behind the diaphragm is then clearly seen; a mass in the posterior or anterior part of the thorax superimposed upon the hilar shadows in the anteroposterior view will appear in its proper position in the lateral view, and broad thin portions will be easily seen as the rays pass through them in the diameter of their greatest density. Emphysematous blebs, which are easily overlooked in the anteroposterior roentgenogram, may become distinctly visible in the lateral roentgenogram. Unusually dense regions which appear as a homogeneous mass in roentgenograms taken in the routine manner may, when taken with higher penetration and the Bucky-Potter diaphragm, demonstrate their true structure, such as calcification or cavity formation.

It is often necessary, Holmes concludes, to take roentgenograms with the patient in the upright or prone position or lying on one side or the other, and before and after expectoration in order to demonstrate the presence of cavities, dilated bronchi, or to determine the size and character of the walls of cavities.

The bronchographic aspect of malignant bronchial stenosis was the subject of an address before the Fifth International Congress of Radiology by Pedro L. Farinas.³ According to Farinas, this varies with the type of tumor. The polypoid type, growing toward the lumen of the bronchus, produces a well localized, more or less round or irregular stenosis with ragged borders and it is characterized in the bronchogram as a "negative shadow"; the tumefaction displaces the opaque oil, creating a filling defect in the shadow cast by this medium. Benign polyps of the bronchus produce a similar image, but the edges are regular and well defined in contradistinction to the irregular edge which is characteristic of malignancy. Below the stenosis, Farinas observed, dilatations of the involved bronchi can be noted. Masses of mucus adherent to the bronchial wall may produce shadows similar to those of the benign tumor, but they are generally multiple, change their appearance at different moments during the examination, and bronchial dilatations are not seen below the stenosis, as they are in tumor involvement. The infiltrating type of tumor produces a concentric filling defect with irregular borders and apparent fixation.

Farinas believes that complete obstruction of the bronchus is a late sign, found during the advanced stage of the process; in such cases it is necessary to continue injection of the iodized oil during the roentgenoscopic examination in order to fill and afford visualization of the constricted portion. Inflammatory processes involving the bronchial wall may present a roentgenoscopic appearance similar to that of the infiltrating type of tumor. The draining bronchus of a pulmonary abscess, for example, exhibits an extended and irregular stenosis but, when closely observed, it lacks the rigidity of the malignant infiltration. The

pus and iodized oil in the lumen of the bronchus often result in imparting a mottled appearance to the narrowed portion of the inflammatory lesion.

"Bronchiectasis is a fairly common disease and there is a well-founded impression that most of the cases of adult bronchiectasis have their inception in early life," states an editorial in the *American Journal of Roentgenology and Radium Therapy*.² The editorial suggests that "it is therefore of considerable importance that the disease be recognized in children so that some of the more extensive cases which are seen late in life may be avoided." The editorial is based on a study of Antoinette Raia undertaken with the object of finding the essential causes which contribute to the formation of bronchiectasis and of discovering the earliest clinical picture which requires watching. From a detailed study of the history, symptoms, physical signs and roentgenograms by which the fundamental factors leading to a diagnosis of bronchiectasis were analyzed, Raia¹⁰ concluded that there are three distinct groups: (1) the group having well established bronchiectasis, (2) the group having early or minimal bronchiectasis and (3) the group having a peribronchiectatic condition or potential bronchiectasis. The main interest of the study lay in the second and third group, whereby a careful examination of its members and the institution of proper treatment, the development of frank bronchiectasis might be obviated.

There were 33 patients who had definite bronchiectasis, and it was from study of these patients that certain criteria were established or recognized for the detection of the early and the potential stages of bronchiectasis. In studying the patients having frank bronchiectasis, it was discovered that more than half of them had a history of pneumonia and that a large percentage had had pertussis and measles. The condition of a few patients resulted from stenosis incident to pressure from a tuberculous lymph node, and post-tonsillectomy abscesses accounted for the illness of 3 of the group. Bronchiectasis afflicting a small number of patients resulted from the lodgment of a foreign body in one of the bronchi with resultant infection, fibrosis and obstruction to the drainage of the lung. The outstanding symptom was cough and expectoration associated with the usual physical signs, such as impaired resonance and bronchial breathing; but often the extent of the bronchiectatic process could be determined only from the bronchogram.

The roentgenologic findings in the study of these patients were of considerable importance because it was from roentgenograms and bronchograms that the ultimate diagnoses were finally determined. Ordinary roentgenographic study of the thorax many times revealed only regions of parenchymal consolidation, principally in the lower lobes, with a tendency to obliteration of the cardiophrenic angles; occasionally the pneumonic consolidations were disseminated throughout and were more or less of the nodular type of infiltration. Roentgenographic study of some patients disclosed evidence of cavitation with interlobar thickenings and clouding of the pleura, at times sufficient to obscure the underlying pulmonary disease. The fibrosis was occasionally so extensive, the editorial points out, as to result in displacement of the mediastinum.

The outstanding roentgenologic observation was persistent pulmonary

infiltration with fibrosis; the honeycomb appearance which is often described as pathognomonic of bronchiectasis was not so frequently observed. Study of some patients disclosed few roentgenographic signs, but their clinical histories pointed to bronchiectasis and the true nature of the disease was definitely established by means of bronchoscopic studies. The bronchogram made during the early or minimal type of bronchiectasis revealed slight pulmonary damage; it revealed bronchiectasis of the saccular type as afflicting a majority of patients, of the cylindric type as afflicting a few patients, and of the combined type as afflicting many patients.

The majority of the patients in this group were suffering from involvement of the left lower lobe of the lung, and this selectivity was the result of anatomic factors which produced mechanical obstruction more readily on the left side than on the right. The right bronchus, according to Duken and von den Steinen,¹ takes a more vertical course than that of the left bronchus and therefore is less angulated. The vast majority of those patients who had frank bronchiectasis also had paranasal sinus involvement, emphasizing the importance of examination of the paranasal sinuses of all children having thoracic symptoms.

Because Raia's study revealed that the group of children who had minimal involvement had a much better prognosis and also that within this group considerable restoration of the lung to a more nearly normal state might be expected, Raia emphasized the importance of recognition of this type of involvement and institution of early, adequate and intensive treatment during the initial pneumonia, so that many of these unfortunate children might be saved from frank bronchiectasis.

It was of interest, according to this editorial in the American Journal of Roentgenology and Radium Therapy, in studying the relationship of the degree of fibrosis of the lungs to the age incidence of pneumonia, measles and pertussis, to note that the younger the patient, when one or a combination of these illnesses occurred, the more marked was the fibrosis; and that the rapidity with which one of these three diseases followed the other also determined the degree of fibrosis. As would be expected, the group of patients whose symptoms dated from an attack of pneumonia were those most likely to suffer from an increase in bronchial markings, while those who had no symptoms following pneumonia usually exhibited negative roentgenograms. It was of considerable importance that the group of patients who had had pneumonia, and whose roentgenograms did not show a tendency toward a complete disappearance of the process, should be carefully watched and studied in order to prevent the occurrence of a bronchiectasis. It is the recognition of this "subacute pathological state," as the editorial calls it, which is particularly important, because the illnesses of these patients represented the so-called potential type of bronchiectasis. The editorial concluded by saying: "It is the recognition of these early changes in the chest seen in roentgenograms that may prevent the subsequent development of a frank bronchiectasis with its long drawn out train of symptoms and debility."

Although much has been written on the subject of emphysema, very few roentgenologic findings characteristic of the disease have been described. O'Donoghue found that only in typical, far-advanced cases afflicting individuals with barrel-chests is the diagnosis made ordinarily

on clinical evidences. He considered this point well illustrated in the number of cases noted in the literature in which the patients at one time or another were treated for cardiac lesions. Although the roentgenologic manifestations were helpful in his experience in the study of this disorder, those seen following the injection of radiopaque oil were either constant or pathognomonic. By means of the intratracheal injection of radiopaque oil it was possible clearly to demonstrate definite evidence of alveolar disorganization, unusual distention of the terminal vesicular structure and alteration in the function, in patients having emphysema.

The term "emphysema" in its broad sense, O'Donoghue⁷ explains, denotes any condition in which there is unusual distention of the pulmonary alveoli with air; this may be local or general and does not necessarily imply permanent injury to the alveolar structure. For example, acute emphysema may follow rapid deep breathing from violent exercise, such as lifting or blowing and it is characterized by a general distention of the alveoli and a rapid return to normal following the removal of the cause. There is merely an increase in the residual air and no permanent damage to the lung structure. In the pressure of compensatory emphysema there is an overdistention of a part of the lung, caused by disease which obliterates the function of a portion of the lung; but the distention may occur in the opposite lung when one lung is compressed or destroyed, or its respiratory function is otherwise inhibited. This type of emphysema also is temporary and does not result in permanent damage to the tissues. Obstructive emphysema likewise may result in overdistention of the unobstructed portion of the lung, but does not produce permanent damage. On relief of the obstruction, the alveolar structure promptly returns to normal. O'Donoghue considers senile emphysema to be part of an atrophic change that occurs throughout the body with advancing years; the alveolar walls become thin, they often rupture and the lungs lose their elasticity. But, in contrast to the true emphysema, the lungs are usually small and contracted. O'Donoghue has adopted the classification of Kountz and Alexander of true (substantive) emphysema in which three important pathologic changes occur: (1) great distention of the alveoli; (2) atrophy and rupture of the walls of the alveoli; (3) obliteration of numerous capillaries. Patients are divided into two groups: (1) those who have constant symptoms of the disease, reduced vital capacity, impaired oxygen saturation of the arterial blood and elevation of the intrapleural pressure, and (2) those in whom the inspiratory position of the thorax is assumed, in which the patients have no constant symptoms, have a normal vital capacity, a normal position and excursion of the diaphragm, and whose oxygen saturation of the arterial blood is within normal limits.

O'Donoghue limited his discussion to the substantive type of emphysema, in the presence of which, after the alveolar structure has undergone permanent changes, very little if anything can be accomplished to restore its normal function. When the lungs are permanently distended, they fail to collapse even when the thorax is open. Anatomico-pathologic study of such lungs reveals thin-walled blebs over the surface of the pleura and bullæ throughout the lung substance. These represent localized air pockets on the surface or within the lung substance.

A review of the literature which O'Donoghue made revealed the following roentgenologic manifestations: (1) generalized increased brilliancy of the lung fields, and a lack of change of radiolucency of the lungs during respiration; normally during inspiration the roentgenoscopic screen lights up, while during expiration it becomes darkened; in the presence of emphysema there is often no demonstrable change in the brilliancy during inspiration or expiration. Frequently at the end of expiration in emphysema, the bases of the lungs fail to be darkened, as they are in normal persons; (2) a low, flattened diaphragm, often scalloped or "tented" in appearance, caused by either the downward ballooning of the lungs, the uniform expansion of which is prevented by the less pliable and less elastic bronchial tissue, or by adhesions of the pleura at the diaphragm; (3) increased space between the heart and the sternum, in the lateral position, which remains essentially unaltered during expiration and inspiration; (4) increase in the prominence of pulmonary markings of the peripheral lung zone, forming a network which extends to the pleural surface; (5) relative or absolute increase in the thickness and density of the larger vessels toward the root of the lungs; (6) impression of diminution in the size of the cardiac shadow, the result of increase in the width of the thorax; (7) transverse diameter of the thorax in the left anterior oblique (45 degrees) roentgenogram often actually is greater than the transverse diameter of the postero-anterior roentgenogram at the same level; (8) scalloped or ballooned-out appearance of the soft tissues in the intercostal spaces when the thorax is visualized in an oblique view; (9) flaring of the ribs with tendency to form a more obtuse angle inferiorly at the costovertebral junction; (10) increase in the width of the intercostal spaces; (11) abnormal enlargement of the lower part of the thoracic cage; (12) annular shadows forming regions of radiolucency in various parts of the lung; (13) hypertrophy of the pectoralis muscle may cause a loss of translucency across the middle lung fields; the scaleni muscles may also hypertrophy and cause apparent loss of translucency of the apices; (14) a roentgenologic comparison of the cubicle measurements of the chest at the height of inspiration and expiration as described by Fray⁵ (double exposure roentgenograms taken at the height of inspiration and expiration to obtain an index of the degree of impairment of pulmonary ventilation and the changes of vital capacity) show a high degree of correlation of findings when the roentgenologic thoracic volume at maximum inspiration is compared with the vital capacity.

O'Donoghue found the changes observed of emphysematous lungs following the instillation of radiopaque oil to be the most characteristic and the most dependable of all roentgenologic signs.

In the normal lung, radiopaque oil, obeying the law of gravity, fills all the bronchioles supplied by the infected bronchus. After a short interval (5 to 10 minutes) the oil enters the terminal air sacs, producing in the roentgenogram the appearance of a branch of a tree at full bloom. Further examination several hours later will reveal the major portion of the oil to be still evenly distributed throughout the alveolar structure.

In those patients who have permanent distention and disorganization or destruction of the alveoli (substantive emphysema), when the opaque oil is injected, the bronchi appear spread out, barren and widely separated from one another, O'Donoghue points out. They are sometimes

curved or bent, due to pressure from neighboring bullæ. The preterminal bronchioles often fail completely to fill. They may end abruptly, or may extend in more or less irregular, narrow pipe-lines to isolated clusters of normal alveoli which have escaped occlusion and disorganization. The filling of the alveolar structure may require many hours or it may never occur at all in the involved region. Rarely, if ever, has any of the oil been seen to enter emphysematous blebs. The lobules and alveoli are conspicuous by their absence. Further examination of patients having this type of emphysema several hours after the instillation of the opaque medium discloses more strikingly the scantily filled alveoli with large intervening regions of alveolar disorganization or distention.

If the person is normal, the oil will remain for months in the alveolar structure. But in the case of the emphysematous patient, most of the oil is expelled by coughing within an hour or so. The difference between the normal and the emphysematous lung, after the oil is expectorated, O'Donoghue believes, is striking. In the presence of emphysema there is an irregular and scattered distribution of the oil-filled alveoli, with large regions of alveolar disorganization or occlusion intervening. The end-result is not the appearance of a tree at full bloom, but rather that of tattered and torn foliage; a tree which has been largely stripped of its leaves. These manifestations, O'Donoghue concludes, illustrate well the evidence of the pathologic process. They demonstrate the extent of the dead air space present and the degree of involvement of the functioning alveolar tissue.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 20, 1939

Response of Cardiac Muscle Cells in Tissue Culture to Mechanical and Chemical Stimuli. G. S. DE RENYI and M. J. HOGUE (Department of Anatomy, University of Pennsylvania). Tissue cultures of chick embryo hearts were used in which the cardiac muscle cells formed a thin transparent plate. With microdissection methods it was found that the large majority of migrating muscle cells do not possess protoplasmic connections with the neighboring cells. The cells are in side-to-side contact. When one cell was stimulated by mechanical or chem-

ical means contraction occurred in a remote part of the culture, *i. e.*, in the explant. We conclude that protoplasmic connections are not essential in conducting certain types of stimuli. Surface contact between the cells seems to be sufficient to propagate the stimulus from one cell to another for a long distance.

Slow Adaptations to Climatic Conditions in the Heat Exchanges in Man. A. C. BURTON, H. C. BAZETT, and J. C. SCOTT (Departments of Physiology of the University of Pennsylvania and the Hahnemann Medical College). Experiments have been made in which the subjects remained for several days in an air-conditioned room set to hot and to cool conditions.

The average daily caloric intake did not differ significantly between hot and comfortable conditions, but increased immediately by over 20% in the cold, more heating foods of a lower equivalent R. Q. being chosen by the subjects. Basal metabolic rates did not alter correspondingly and there was no manifest shivering. Caloric intake was greater, under the same thermal conditions, in winter experiments than in summer.

Day and night evaporative losses, calculated from changes of weight, showed a rise for the first few days of heat followed by a fall. In summer, the initial rising phase was shortened. In the following cold period evaporation fell to an abnormally low minimum on the second or third day to rise finally to normal values for this temperature.

The blood flow in the finger showed a steady increase for 5 days of heat. Artificial heating of the legs produced, not the usual reflex increase of flow, but a decrease. This effect diminished as adaptation proceeded. In the first 2 days of cold following a hot period, flow remained far above the normal constriction values which were reached later.

Body weight increased in the hot periods, and decreased after a large and persistent diuresis when the temperature was lowered.

These findings suggest that acclimatization to heat is accompanied by a shift of heat loss from evaporation towards radiation and convection, associated with an increasing peripheral circulation. The latter may depend upon compensatory vasoconstriction, but its maintenance involves less strain upon the organisms after changes of fluid balance, and probably of blood volume, have taken place.

Adaptation to Climate and Its Effects on the Cardiovascular System. H. C. BAZETT and J. C. SCOTT (Departments of Physiology of the University of Pennsylvania and Hahnemann Medical College). Continued exposure to warmth is associated with considerable changes in the circulation. Those here reported represent observations on subjects in the experiments already described in relation to heat loss. Since no progressive increases in cardiac outputs with the subjects lying down were observed in the warmth to parallel the changes observed in the circulation in the fingers, these presumably depended on alterations in distribution. On the other hand, in the standing posture cardiac outputs differed considerably in heat-adapted and cold-adapted individuals. In a series of 42 observations on two subjects the mean values in the warmth were 1.95 ± 0.24 (standard deviation) liters per square meter per minute under basal conditions and 1.95 ± 0.15 non-basal in the

afternoon; on the other hand, when these subjects were cold-adapted the values averaged 1.63 ± 0.17 and 1.79 ± 0.17 respectively. The differences have statistical significance. Consequently conflicts in the literature presumably depend at least partly on the condition of the subjects. Dehydration, particularly in the morning, was associated with reduction in the cardiac output in the standing posture.

Systolic blood pressures were increased at first in the warmth and were later reduced; they were reduced at first in the cold and then later raised. Blood pressures are increased at the same normal room temperature following a previous long exposure to warmth. The difference between lying and standing pulse rates was at first increased in the warmth, later decreased, at first decreased in the cold and later increased. Cardiovascular fitness (as estimated by changes in pulse rate and systolic blood pressure on standing) usually was improved above control levels at the end of adaptation to heat, though it was lowered in the initial stages of exposure and also if dehydration was present. Fitness so estimated was greater in the morning on rising than in the afternoon, even in the cold where reduction of cardiac output was greater in the morning. The same subject might show a daily decrease of "fitness" in the morning while showing an increase in fitness in the afternoon. No reason for such conflicting changes was found.

The Pressor Effects of Heterologous Injections of Heated Kidney Extracts. E. M. LANDIS, W. A. JEFFERS and E. SHIELS (Laboratory of Pharmacology and Robinette Foundation, University of Pennsylvania). Using a method previously described (J. Clin. Invest., 17, 189, 1938), we prepared 10% aqueous extracts from the kidneys of rats, guinea pigs, rabbits, dogs and man. These extracts, preserved by freezing and desiccation *in vacuo* ("Cryochem" process), were redissolved, centrifuged, and then immediately injected intravenously into rats, guinea pigs, rabbits and dogs under light nembutal anesthesia, and also into unanesthetized rabbits. Dosage was adjusted so that each animal, according to body weight, received an equivalent volume of fluid and amount of solid extract. Because of diminishing response with rapidly repeated injections, each animal received but 1 dose except for the observations on dogs, in which injections were given at intervals of 1 hour.

The pressor effects of the respective extracts were not species-specific, since each extract raised the blood pressure to some degree in all four species. However, the potency of the extracts differed according to species in that extracts of rabbits' kidneys were most active throughout while those of human kidneys were usually almost inactive, with rat and guinea pig extracts in an intermediate position as to potency. The final extracts all contained approximately 0.10% albumin and 0.12% globulin. Pressor activity was not directly related to the amount of globulin present. The results of ammonium sulphate precipitation followed by suitable dialysis indicate that heating to 55°C ., while diminishing depressor and toxic effects, also precipitates or destroys at least some of the pressor substance, particularly in the kidney extracts of dog and man.

Autonomic Innervation of the Face. F. H., LEWY, R. A. GROFF, and F. C. GRANT, (Harrison Department of Surgical Research and the Neurosurgical Clinic, University of Pennsylvania). A moving picture is demonstrated showing that in the cat the autonomic innervation of eyelid, whiskers and tongue after denervation of the corresponding muscles (Vulpian-Heidenhain-Sherrington phenomenon) is two-fold in origin, *i. e.*, parasympathetic and sympathetic. The sympathetics act also on non-denervated muscles. Both actions supplement each other. The parasympathetic action is best seen after injection of acetylcholine, but also after nicotine. The same parasympathetic reaction is produced by electric stimulation of the Gasserian ganglion following section of the trigeminal root and denervation. Serial sections showed that the impulses for the eyelid phenomenon run over the first trigeminal division, for the whisker movements over the second division, for tongue movements over the chorda tympani. The origin of these efferent parasympathetic fibers was found by retrograde degeneration to be in the mesencephalic trigeminal nucleus.

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ORIGINAL ARTICLES.

EXOGENOUS PERNICIOUS ANEMIA.

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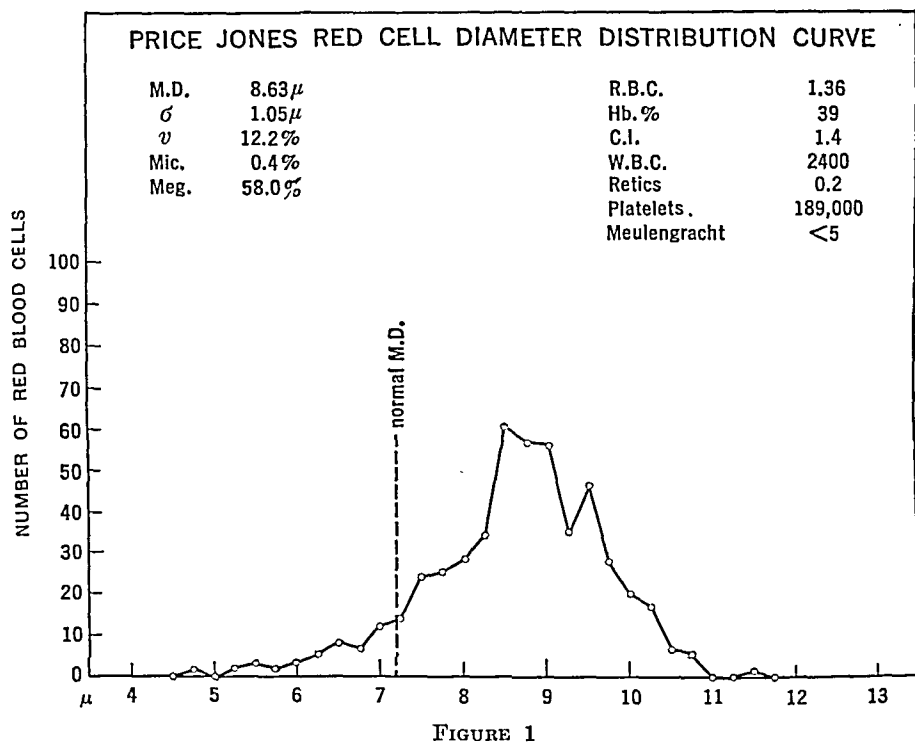
(FROM MEDICAL DEPARTMENT B., BISPEBJERG HOSPITAL.)

ACCORDING to the present pathogenetic concept, pernicious anemia may be regarded as a deficiency disease. Development of anemia is due to deficiency of antianemic factor, as hemopoiesis cannot be normally completed without the concurrence of this substance. The chemical constitution of the antianemic factor has not been clearly defined until now; Castle and co-workers²⁻⁵ in their fundamental experiments, however, have shown that it is produced by interaction between an intrinsic factor, found in normal gastric juice, and an extrinsic factor, conveyed by the food. The exact location of this interaction has not been definitely settled; Meulengracht's^{12a} experiments, however, show that "intrinsic factor" is produced by the pyloric glands of the stomach and the Brunner glands in the duodenum. As mentioned, "extrinsic factor" is supplied by the food, especially by meat, milk and eggs; most amply it is to be found in brewer's yeast and liver, in the latter, simultaneously with finished antianemic factor. While "intrinsic factor" very likely can be conceived as an enzyme, "extrinsic factor" seems to be more related to the vitamins; the latter is frequently derived from the same sources as the vitamin-B₂ complex, yet it is, apparently, different from both vitamin-B₆, lactoflavin and nicotinic acid.

In the pathogenesis of true Addisonian anemia the deficiency of antianemic factor is presumed to be caused by lack of "intrinsic factor;" the disease may accordingly be regarded as an endogenous condition; several facts, however, imply that the deficiency is more of quantitative than of qualitative nature. Of the primary cause of the deficiency, and especially of the rôle played in pathogenesis by the concomitant gastric anacidity, nothing definite is yet known. Extensive gastric resections now and then are followed by pernicious anemia; this may also happen subsequent to corrosion of the gastric

mucosa;^{1b} the importance of quantitative factors seems thus to be proven. The most recent investigations by Meulengracht^{12b} and by Magnus and Ungley¹¹ render it likely, however, that purely quantitative factors are not alone responsible for the production of "intrinsic factor" sufficient to prevent pernicious anemia.

Even in unimpaired production of "intrinsic factor," deficiency of finished antianemic factor may occur; this happens when intestinal absorption is lowered, as in idiopathic steatorrhea and intestinal strictures. At least in the beginning of these conditions a sufficient amount of antianemic factor is supposedly produced; absorption being impaired, however, macrocytic anemia develops with an aspect



of the blood, hardly differing from the one found in true pernicious anemia.

The mentioned anemic conditions and their pathogenesis are fairly well known and they occur, if not frequently, yet in a considerable number. In contrast, only sparse and in part uncertain information can be obtained on the anemic condition in which deficiency of antianemic factor is due exclusively to lack of "extrinsic factor," a condition which might properly be termed: *exogenous pernicious anemia*. In temperate climates, at any rate, such cases seem to be extremely rare; whereas in the tropics, according to Wills,¹⁵ they occur more frequently; in the tropics, however, conditions are diffi-

cult to judge; it is often impossible to detect the single dietary deficiency, causing anemia, and, furthermore, various infections may influence the aspect of the blood.

In the literature, however, a certain number of publications exist, dealing with cases of pernicious anemia with free hydrochloric acid in the stomach. In 1934 I^{1a} collected all cases then in existence; having critically excluded the major part of them, I found that the remaining cases still amounted to 32; to this number I added 2 cases of my own, the first of which was reported in detail. It cannot be ruled out, however, that a number even of those cases, in spite of all critical judgment, are not true cases of pernicious anemia, but cases of other diseases, most likely leukosis and idiopathic steator-

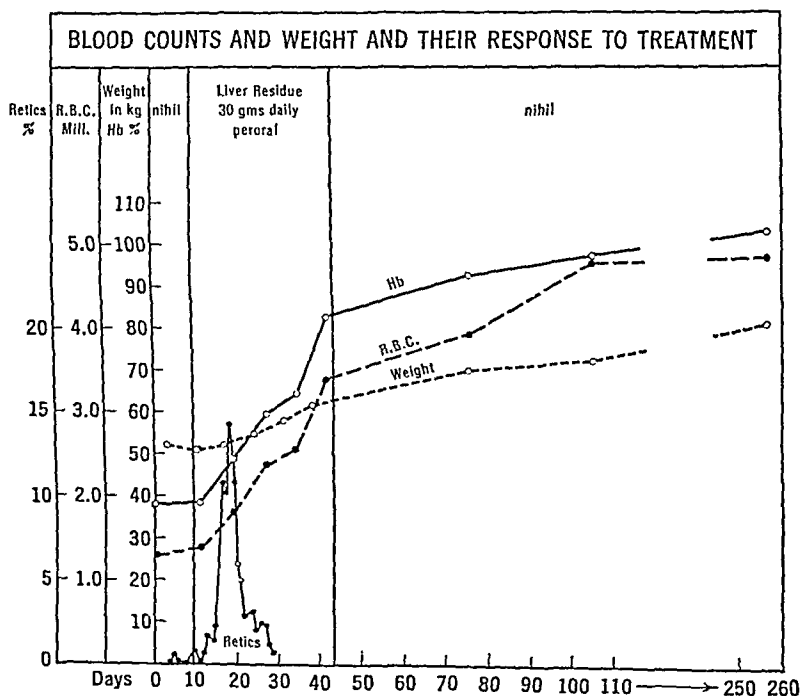


FIGURE 2

rhea. Yet, in a few of the mentioned cases, *e.g.*, in the first of my own 2 cases, many facts make it highly likely that anemia is due to deficiency exclusively of "extrinsic factor" in the food.*

This pathogenetic connection was, of course, not discovered until very recently, and in this period but few observations can be traced on such cases of pernicious anemia, due to dietary deficiency. Besides in my own first recorded case,^{1a} a definite dietary deficiency was demonstrated in 3 cases, published by Ungley in 1933^{14a} and

* It can be mentioned that in 1931, R. A. Kern ("Diet as a Factor in the Etiology of Anemia," *Ann. Int. Med.*, 5, 729, 1931) made the suggestion, supported by clinical evidence, that "in rare instances an Addisonian type of blood picture may result in a patient whose diet is deficient in the *extrinsic factor*."—EDITOR.

1938,^{14b} and in 2 cases, recorded by Groen and Snapper⁷ in 1937. Yet, all of these cases in various important respects differed from typical Addisonian anemia and in all of the cases complete remission did not occur before treatment was instituted with preparations, effective also in ordinary pernicious anemia, *i.e.*, containing finished antianemic factor. Complete evidence of the importance of dietary deficiency will not be had, however, before complete remission is obtained by treatment exclusively with "extrinsic factor." A case of this sort is here recorded.

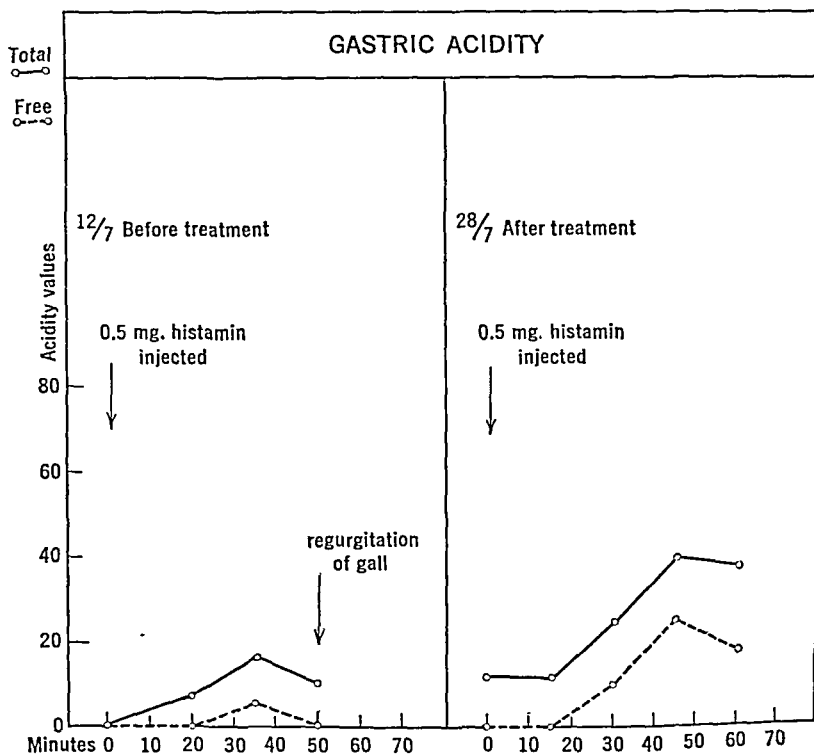


FIGURE 3

Case Report. A male patient, aged 43, was admitted to this hospital on July 1, 1937 because of pernicious anemia. No family history of blood diseases; the history was as a whole negative until 1930 when the patient began to suffer from constipation. He felt rather embarrassed and that is why he radically changed his diet, eating from that time nothing but white bread, butter, porridge, cream and a single egg daily; once in a while he had a few fish-balls, vegetables and fruits, but never any sort of meat, liver, or milk. On this diet his constipation improved, his stools became daily, spontaneous, of natural color, not very bulky, and there never was diarrhea. The general condition of the patient was on the whole satisfactory and he was able to attend to his work as an electrometer controller.

Four to five months prior to admission, however, he began to suffer from fatigue; at the same time he grew meagre and became pale to an extent that it was discovered by his surroundings. Yet, he continued his work until 10 days before admission, when he had to stay in bed because of overwhelming fatigue and increasing dyspnea on exertion. He suffered some-

what from soreness of the tongue, but never had any acroparesthesia. Apart from these complaints the patient had no subjective symptoms.

The physical examination revealed an emaciated and extremely anemic patient, with a dubious icteric tinge. The surface of the tongue was smooth and glistening, practically no papillæ remaining. The rest of the physical examination revealed nothing abnormal; especially no signs were found of organic nervous disease, no optical neuritis and no pellagroid skin changes.

In the urine nothing abnormal was found; the benzidine reaction in feces was negative, as was the Wassermann reaction. The sedimentation rate of the blood was 82 mm. in 1 hour. Ewald test meal, $\frac{3}{4}$ hour, July 8: 84 + 33 cc., free acid: 5, total acidity: 30, + lactic acid. The result of titration of gastric secretions after injection of histamin is shown in Figure 3.

Hematological findings, July 2: Icteric index (Meulengracht): < 5. Hemoglobin percentage (100% = 18.5% O₂): 39. R.B.C.: 1,300,000. Color Index: 1.5. Leukocytes: 3200. Platelets: 106,000. Differential count, July 13: segmented neutrophils, 44%; lymphocytes, 50%; monocytes, 4%; eosinophils, 1%; basophils, 1%. Nuclei of all leukocytes were highly segmented, no stabs. The red cells showed anisocytosis and poikilocytosis; no nucleated red cells. Price-Jones red cell diameter distribution curve (July 13, Dr. E. Mogensen) is shown in Figure 1. Sternal puncture (July 13, Dr. Engelbreth-Holm): bone-marrow full of cells, of which 35.7% were immature red cells (hemocytoblasts, 4%; promegaloblasts, 16%; megaloblasts, 60%; cells in mitosis, 2%; normoblasts, 18%). Of the white cells there were: myeloblasts, 2.3%; promyelocytes, 13.7%; myelocytes, 12%; metamyelocytes, 34%; segmented, 26.7%; monocytes, 0.3%; lymphocytes, 9.7%; plasma cells, 1.3%. No eosinophils were observed. Several of the myelocytes were strikingly big, and their nuclei in many cases showed a typical hypersegmentation. In the histologic preparation from the clot was found plenty of bone-marrow with considerable cellular hyperplasia, practically no fat cells being observed. There were many megaloblasts and promegaloblasts, typical of pernicious anemia.

Microscopic diagnosis: *anæmia perniciosa*.

TABLE 1.—ANALYSIS OF FECES IN PER CENT.

	July 14	July 14	July 15
Dry Matter	34.9	32.4	32.8
Substances, soluble in gasoline (neutral fat + free fatty acid)	4.6	4.3	4.4
Neutral fat	2.9	2.2	2.3
Free fatty acid, calculated as oleic acid	1.7	2.1	2.1
Substances, ether extractive only after treatment with hydrochloric acid (bound fatty acid)	1.0	2.8	2.4

Blood sugar tolerance curve after ingestion of 70 gm. of glucose: rise from 86 mg. % to 120 mg. % during one-half hour. Calcium in serum: 9.7 mg. %, 9.5 mg. %. Radiological examination of skeleton showed no halisteresis, and of stomach, duodenum and intestinal tract showed nothing abnormal. Following Lunn's method,¹⁰ a detailed dietary history was obtained, showing that the patient through his diet, hardly changed during 7 to 8 years, had had the following average daily intake:

TABLE 2.—AVERAGE DAILY INTAKE.

		Minimum requirements.
Vitamin A:	3300 int. units	1500
Vitamin B ₁ :	228 int. units	300
Vitamin B ₂ :	380 int. units	?
Vitamin C:	515 int. units	600
Calcium:	0.38 gm.	0.60
Phosphorus:	0.97 gm.	1.30

From this it is evident that the patient had been subminimally covered as to B₁ and C, and in definite deficiency as to Ca and P.

These findings made it likely that the anemia was due to a deficiency of "extrinsic factor," no other dietary deficiency of importance being substantiated. I therefore resolved to attempt a treatment exclusively with plenty of ordinary food, together with "extrinsic factor." The latter was given in form of liver residue, as we at that time had a preparation of that sort which in 3 cases of untreated pernicious anemia was shown to contain plenty of "extrinsic factor," but no finished antianemic factor at all. This preparation was used from July 12 to August 14 (10 gm. 3 times daily with the meals). At no other time was any other medical preparation given, apart from mild hypnotics. As seen in Figure 2 a typical reticulocyte response quickly set in and during the following month the anemia showed complete remission. The weight rose by 50% and the sedimentation reaction fell to 8 mm. After 18 days the patient was able to be out of bed and walk about without any trouble. The surface of his tongue became quite natural, numerous new and normal papillae sprouting forth.

It should be specially mentioned that the gastric secretion was completely restored to the normal; before treatment, as mentioned, anacidity existed, being almost completely refractory to histamin, as shown in Figure 3. Already after 15 days' treatment with "extrinsic factor" free hydrochloric acid was found in the stomach after injection of histamin (Fig. 3). Ewald test meal, $\frac{3}{4}$ h., July 27: 35 + 31 cc., free acid: 48, total acidity: 75, no lactic acid. Ewald test meal, $\frac{3}{4}$ h., Aug. 14: 15 + 14 cc., free acid: 52, total acidity: 71.

When discharged from hospital, Aug. 14, the patient felt absolutely well; the hemoglobin percentage was 83, R.B.C.: 3,400,000 and his weight had increased from 51 kg. to 62 kg. He had no constipation and without any trouble ate all sorts of food. Liver residue was discontinued when he was discharged. During the following 7 months the patient was frequently controlled. He ate ordinary food and took no medicine; he had no subjective complaints and attended to his comparatively hard work as an electrometer controller without any difficulty. His appearance was radiant, the surface of the tongue quite natural, and 7 months after discharge from hospital, the hemoglobin percentage was 104; R.B.C.: 4,870,000; and the weight 81.1 kg.

Discussion.—A. *Diagnosis.* On admission, the patient exhibited a clinical picture, practically completely characteristic of true Addisonian anemia. The considerable anemia with the increased color index, the pronounced glossitis, the typical result of the sternal puncture and the classical Price-Jones distribution curve, all these findings spoke conclusively in favor of pernicious anemia. Against this diagnosis there was really nothing but the normal icteric index and the slight amount of free acid in the Ewald test meal; the free acid might, however, be explained by the presence of lactic acid. Yet, after injection of histamin, free acid again was found in the gastric secretion, even if only in a comparatively slight amount. It was really this finding, in connection with the peculiar history, that at first suggested the true cause.

Other macrocytic anemias could hardly be called in question in differential diagnosis. The patient showed no signs of idiopathic steatorrhea; his stools had a normal bulk and color and a normal

content of fat; there was no halisteresis of the bones, the serum showed normal calcium values, and even if the blood sugar tolerance curve after glucose ingestion was rather low, still it was hardly definitely below the normal.

Neither could anemia in intestinal stricture be discussed, the progress of intestinal contents being absolutely normal, as shown by radiologic examination; during his whole stay in the hospital the patient, furthermore, had daily, natural evacuations. Finally, it has to be added that neither parasitic ova nor segments of tapeworm were observed in feces, and that the patient never had been outside Denmark; thus it is clear that he did not carry *bothriocephalus latus*, or other intestinal parasites.

The patient, also, as is evident from the examinations, did not suffer from pellagra, syphilis, tuberculosis, chronic nephritis, Hodgkin's disease or from any other of the diseases that are occasionally accompanied by macrocytic anemia. The diagnosis of pernicious anemia is really the only one left, this diagnosis being furthermore confirmed as well by the characteristic findings, and especially by the further course of the disease.

B. Etiology. The diagnosis thus being established, the slightly preserved gastric acidity and the obvious dietary deficiency in the history called attention, as mentioned above, to the possibility of the etiologic importance of this dietary deficiency. It was characteristic of the patient's dietary restrictions that they chiefly comprised exactly the foods, containing "extrinsic factor;" apart from the amount of "extrinsic factor," supplied by the patient's modest consumption of eggs, his diet during 7 to 8 years seems to have been entirely deprived of "extrinsic factor."

Even if there were no support for the suggestion, it could not *a priori* be excluded that other dietary deficiencies, in particular avitaminosis, might have been at least contributory to the development of anemia. The minute dietary history showed, however, that the patient had been fairly well covered as to the generally known vitamins, and in deficiency only as to Ca and P.

This supports my concept of the lack of "extrinsic factor" as the only etiologic factor. The complete evidence of this was obtained when a typical reticulocyte response and complete remission of the blood values followed as an immediate result of treatment with nothing but "extrinsic factor" and plenty of ordinary food.

This is the place once more to emphasize that the applied "extrinsic factor"-preparation, consisting of liver residue (*i.e.*, what remains of whole liver when, in the production of commercial liver extract, all antianemic factor has been extracted), in the same amounts as the prescribed ones had been used in 3 cases of untreated pernicious anemia without provoking any reticulocyte response, nor increase of the blood counts.

My concept of the etiology of the anemia was thus completely

confirmed; the only source of error, yet remaining, was that the remission might be explained as spontaneous. This possibility, however, was entirely eliminated when the patient, 7 months after the discontinuation of treatment, showed a hemoglobin percentage and a weight which were still increasing, in spite of the fact that he did not take any medicine at all, but only continued to eat ample amounts of an ordinary, but sufficient, diet.

C. Pathogenesis. Special interest attaches to the fact that the gastric secretion was restored to normal during treatment. Even if a few observations on similar cases do exist,^{6,8a,b,13} this is most unusual in ordinary endogenous pernicious anemia. It is most likely that in this case achylia was a reversible process; that is why the anacidity hardly can have been caused by the usual atrophic gastritis; it may sooner have been of functional nature. It must not be forgotten, however, that even highly developed anatomical changes may be reversible, *e.g.*, the atrophic glossitis, as seen in this patient, and frequently present both in ordinary pernicious anemia and pellagra. In a similar way, Jones, Benedict and Hampton's⁹ gastroscopic studies have shown that even gastritis in pernicious anemia to a certain extent is a reversible process.

As to the restored acid secretion in the stomach, complete accordance exists between this patient, Groen and Snapper's⁷ 2 cases and my own previous case,^{1a} in all of which treatment was followed by complete restoration of gastric acidity. It is evident that in this respect exogenous pernicious anemia shows close resemblance to idiopathic steatorrhea.

Facts observed in the above published case, combined with generally known facts, make it likely that an absolute or relative deficiency of "extrinsic factor," continuous during a protracted period, causes gastric anacidity or achylia, this being, however, to a certain extent a reversible process. As to the rôle played by dietary deficiency and subsequent achylia, in the pathogenesis of Addisonian anemia, nothing definite can yet be stated. It is probable, however, that a vicious circle is established by the development of achylia, this causing an impaired absorption both of "extrinsic factor," already scantily supplied, and of the eventually formed antianemic factor. In this way, conditions are provided for the development of true pernicious anemia, the achylia being finally no longer reversible and the production of "intrinsic factor" checked. It is possible that development of true pernicious anemia, at least in the beginning, is caused by either an absolute or relative deficiency of "extrinsic factor," this theory being supported both by Ungley's^{14a} work and by the above mentioned case.

The development in this patient, not of an endogenous irreversible pernicious anemia, but of an exogenous reversible pernicious anemia may be explained by the extremely pronounced deficiency of "extrinsic factor." During 7 to 8 years practically no "extrinsic

factor" was conveyed to the patient, who nevertheless got along fairly well; at the moment achylia developed, however, the impairment of absorption caused quick derangement, this being even so quick that the organic changes in the gastric mucosa did not find time to develop to the extent of becoming irreversible before specific treatment was instituted.

In my patient, without any reasonable doubt anemia was due alone to the dietary deficiency; it developed at a time when the achylia was still reversible and production of "intrinsic factor" not yet checked. This explains the satisfactory and lasting result of the treatment, and it seems permissible to suppose that the patient is permanently cured, provided that he does not again some day restrict his diet.

Conclusion.—This case report proves the existence of an exogenous form of pernicious anemia, this form being etiologically, pathogenetically and clinically closely related to the true endogenous form, sometimes being even a precursor of the latter. Without doubt it is far more frequent than generally believed; the usual routine treatment of pernicious anemia with liver or stomach preparations, however, will in most cases obscure its existence, these preparations being, of course, equally effective in the endogenous and the exogenous form.

Supposedly all stages exist between the purely exogenous reversible form, of which my patient was a typical example, and the purely endogenous irreversible form, represented by the major part of pernicious anemia patients, it being nothing but a question of different extent and duration if one or the other form is going to develop. It is practically important, however, to distinguish between cases of reversible exogenous pernicious anemia and those of irreversible endogenous pernicious anemia, as the patients, suffering from the former, may be spared from a lifelong treatment which is not only unnecessary, but also troublesome and expensive.

Summary.—A case of pernicious anemia is reported in a man of 43. It is shown that the development of anemia was due to deficiency of "extrinsic factor," continuous during 7 to 8 years. Treatment with "extrinsic factor" exclusively was followed by complete recovery and complete restoration of acid secretion in the stomach. The patient was controlled during 7 months, subsequent to the discontinuation of the specific treatment, and no relapse was observed.

The case is conceived as a case of exogenous pernicious anemia; its etiology and pathogenesis are discussed, as well as its relation to true endogenous pernicious anemia.

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THE PRESENCE OF THE ANTIPERNICIOUS ANEMIA FACTOR IN AN EXTRACT OF FETAL BOVINE LIVERS.

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IN correlating the response to liver therapy with the achylia gastrica in pernicious anemia patients, Castle and his coworkers³⁻⁶ demonstrated that the gastric juice of pernicious anemia patients is relatively deficient in some factor which is present in normal gastric juice. On the basis of these findings, Castle proposed his theory concerning the mechanism of the production of pernicious anemia. This theory has been amply confirmed.^{9-11,13-15,17,20,22} Castle stated that the interaction of some substance in the gastric juice (intrinsic factor) and some dietary principle (extrinsic factor) produces a substance which is absorbed and stored in the liver.¹⁶ According to this theory, a deficiency of the liver factor may result in several ways: (a) lack of the extrinsic factor in the diet; (b) lack of the intrinsic factor in the gastric juice; (c) failure of absorption of the end product of the interaction of the above two factors. To these might be added two more means by which a macrocytic anemia might be produced, as suggested by Goldhamer;⁷ (d) inability of the liver to store the antipernicious anemia substance;^{23a} and (e) inability of the bone marrow to utilize the antipernicious anemia factor.¹²

According to Castle's theory, the liver factor can be produced only by the interaction of the intrinsic and extrinsic factors. The fetus is entirely lacking in the extrinsic factor except for the amniotic fluid and the small amount of detritus which collects in the gastro-

intestinal tract. It is unlikely that either of these serve as sources of the extrinsic factor. Consequently, the fetus either must not require the liver factor or receives it from the mother through the placenta. If Castle's theory does not apply to the fetus, the antipernicious anemia substance may be formed *de novo* by the liver or some other organ.

The purpose of the present investigation is to determine whether the fetal liver contains the antipernicious anemia factor. Its presence in significant amounts would suggest that the fetus requires the factor and furthermore would indicate (assuming Castle's theory to be true) that the mother must produce extra quantities of the factor to provide both herself and the fetus. This possibility would have considerable significance in view of the fact that a macrocytic anemia sometimes accompanies pregnancy.

Methods. An extract of fetal bovine livers was prepared by a method known to yield a potent extract when applied to livers of adult animals. Each cc. of the prepared extract was equivalent to 100 gm. of the fresh livers. The extract contained 7.74% total solids.

Three pernicious anemia patients, 1 in severe relapse, were treated with the fetal liver extract by one of us (O. R.) at the Cook County Hospital. Red and white blood cell counts, reticulocyte counts, and hemoglobin determinations were made in the usual manner.*

Results. CASE 1.—M. Br. (No. 2199), a white female, aged 53, was admitted to the hospital, January 14, 1938. This woman had been discharged 6 months before, after being treated for pernicious anemia. She had not received liver since her discharge. On admission, her blood pressure was 92/64, temperature 100° F., pulse 100. Blood examination revealed 1,960,000 red blood cells per c.mm., poikilocytosis, anisocytosis, 46% hemoglobin (Sahli), and 2400 white blood cells per c.mm. The diagnosis was pernicious anemia in severe relapse. Treatment consisted of intramuscular injections of 0.5 cc. of the experimental extract for 17 days, 0.5 cc. again on the 19th day. On the 20th day 2 cc. were administered, and 2 cc. weekly thereafter for 2 weeks. The total dosage was 15 cc. At the end of 34 days of treatment, the blood picture was 4,270,000 red blood cells per c.mm., 11,000 white blood cells per c.mm., with 79% hemoglobin. There was marked subjective improvement. She was discharged, February 1, 1938, 17 days after admittance.

CASE 2.—M. B. (No. 2570), a colored female, aged 61, was admitted to the hospital, January 16, 1938. On admission, her blood pressure was 130/54, temperature 100.6° F., pulse 104. She complained of diarrhea, projectile vomiting, blood in the stools, and paresthesias of the hands. Physical examination revealed a pale, smooth, sore tongue; the left patellar, abdominal and epigastric reflexes were absent. An examination of the gastric contents following an Ewald test meal revealed no free acid. The blood examination revealed 1,110,000 red blood cells and 3800 white blood cells per c.mm., hemoglobin 25% (Sahli). There was marked anisocytosis and poikilocytosis. The diagnosis was pernicious anemia. Treatment consisted of intramuscular injections of 1.5 cc. of the experimental extract daily for 9 days, then every third day for 5 injections. At the end of this time the patient received 3.6 cc. of a potent horse liver extract. The total dosage was 21 cc. of the experimental extract. The patient improved markedly under treatment; the paresthesias disappeared entirely. At the

* We are indebted to Miss Helen Legere for the laboratory studies.

time of the change from fetal liver to the horse liver concentrate, a blood examination revealed 4,090,000 red blood cells and 4400 white blood cells per c.mm., and 65% hemoglobin.

CASE 3.—B. J. (No. 6391), a white female, aged 68, was admitted to the hospital, February 6, 1938. On admission, her blood pressure was 130/70, temperature 99.5° F., and pulse rate 96. She complained of diarrhea and swelling of both feet. Physical examination revealed an emaciated old woman, lemon yellow in color with a pale atrophic tongue, and a large umbilical hernia. The blood examination revealed 1,360,000 red blood cells and 5600 white blood cells per c.mm., and 34% hemoglobin (Sahli). The diagnosis was pernicious anemia. Treatment consisted of intramuscular injections of the experimental extract, 1.5 cc. daily for 13 days, and 1.5 cc. on the 16th day. The experimental extract having been exhausted, a potent horse liver concentrate was given on the 18th day of treatment. At the time of the injection of the last dose of the experimental extract, blood examination revealed 2,770,000 red blood cells and 4500 white blood cells per c.mm., and 49% hemoglobin.

The response of all 3 patients is typical of the response following the injection of a liver extract containing the antipernicious anemia factor.

Discussion. The prompt reticulocyte responses together with the return to normal blood pictures give undisputable proof of the presence of the antipernicious anemia factor in the fetal bovine livers. If Castle's theory as to the necessity of both the extrinsic and intrinsic factors for the formation of the antipernicious anemia substance is assumed to be true, then we can most reasonably account for the presence of this substance in fetal liver only as the result of its passage through the placenta, since the fetus is not supplied with the extrinsic factor.

A careful search of the literature revealed only 4 previous reports concerning the use of fetal liver in the treatment of pernicious anemia. Berglund, Watkins and Johnson² reported that fetal bovine liver, fed as the desiccated material equivalent to 300 gm. of fresh liver daily, was active in the treatment of 1 case of pernicious anemia. However, the reticulocyte count, which is in part a measure of the bone marrow response to the antipernicious anemia factor, did not rise above 1.8%.

Goldhamer, Isaacs and Sturgis⁸ prepared an extract from the liver of a 7-month human fetus. Twenty cc. of this extract, representing 65 gm. of the fresh tissue, were administered in a single dose. The reticulocyte response reached a maximum of 17.6% on the 7th day, although the hemoglobin declined and the red blood cell count remained unaltered. On the basis of this result the authors concluded: "The active principle necessary for the maturation of red cells is present in the liver at least two months before birth." Because the reticulocyte count is *in itself* no measure of the potency of a liver extract, these results are not conclusive. It is well known that the injection of inactive protein substances and certain drugs will cause a reticulocyte response. Spontaneous rises in the number of reticulocytes as high as that reported by Gold-

hamer *et al.* have been seen in our clinic. The same criticism applies to the one patient observed by Bence.¹

Wintrobe, Kinsey, Blount and Trager²⁴ prepared extracts of fetal pig livers in the age groups of second third, third third, fifth sixth, and last sixth of pregnancy. All of these extracts were without effect in doses of 1 to 10 cc. when administered to pernicious anemia patients. These patients responded subsequently to a commercial liver extract. We cannot adequately account for this apparent difference in the liver factor content of the livers of fetal calves as compared with fetal pigs. The marked differences in placental structure in the cow and pig may account for a difference in permeability of the placentas to the liver factor. The absence of the liver factor from the livers of fetal pigs suggests that the fetus is unable to form this factor *de novo*. It also suggests that the liver factor which is effective in the treatment of pernicious anemia is not required by the fetus for the maturation of red blood cells.

This latter suggestion is further substantiated by the results of Wigodsky and Ivy²¹ with the injection of a potent liver extract into pregnant albino rats in the attempt to reduce the red blood cell size of the newborn. The injection of a liver extract of known potency into pregnant rats as many as 14 days before delivery exerted no significant effect upon the red blood cells of the newborn. Similar results in the rabbit have been reported by Wintrobe *et al.*^{23b} Stasney *et al.*^{18,19} have demonstrated that a concentrate of normal human or swine gastric juice, when injected intraperitoneally into pregnant rats, reduced the red blood cell diameters of the newborn pups.

TABLE 1.—RESPONSE OF 3 PERNICIOUS ANEMIA PATIENTS TO PARENTERAL ADMINISTRATION OF FETAL CALVES' LIVER.*

Pat. No.		Days.														
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	30.
1	Dose, cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	2.0**
	Hb. %†	46.0	48.0	59.0	65.0	79.0
	R.B.C. ‡	1.9	2.1	3.0	3.7	4.3
	W.B.C. §	2.4	4.6	4.8	10.0	11.0
	Retic. %	0.4	0	0.2	1.0	8.0	21.0	15.0	13.0	..	8.0	8.0	3.4	2.0	2.0	..
2	Dose, cc.	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5**
	Hb. %	25.0	28.0	39.0	53.0	65.0
	R.B.C. ‡	1.1	1.3	2.2	3.1	4.1
	W.B.C. §	3.8	13.0	6.3	8.2	4.4
	Retic. %	0.8	0.6	3.0	7.0	17.0	17.0	26.0	49.0	35.0	22.0	21.0	9.0	8.0	2.0	..
3	Dose, cc.	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	..	1.5	**
	Hb. %	34.0	30.0	44.0	49.0	..
	R.B.C. ‡	1.3	1.3	2.2	2.8	..
	W.B.C. §	5.6	3.1	4.8	4.1	..
	Retic. %	0.6	2.0	3.0	6.0	11.0	14.0	..	25.0	29.0	24.0	12.0	4.0	1.4	0.4	..

* 1 cc. of the fetal calves' liver extract was equivalent to 100 gm. of original liver.

** For dosage see protocol of case history.

† Sahli.

‡ Millions per c.mm.

§ Thousands per c.mm.

Assuming that the antipernicious anemia factor will pass from the circulation of the mother to that of the fetus and will be stored in the fetal liver, it is plausible, as suggested by Wintrobe and Shumacker^{23b} that the mother's stores of the liver factor may be so depleted by fetal storage of the factor as to cause a macrocytic anemia during pregnancy.

Experiments are now in progress to determine whether there is any correlation between the amount of liver factor contained in fetal liver and the amount of intrinsic factor present in the fetal stomach.

Summary. 1. The presence of the antipernicious anemia principle in fetal bovine livers is demonstrated by the fact that extracts obtained from this source produced typical, prompt, and definite remissions in 3 pernicious anemia patients.

2. Since the fetus is completely deficient in the extrinsic factor of Castle, the antipernicious anemia factor presumably reached the fetal liver by passing from the circulation of the mother through the placenta into the fetal circulation.

3. These findings support the view that withdrawal of the antipernicious anemia principle by the fetus may be an etiologic factor in the production of a macrocytic anemia of pregnancy.

4. Evidence is discussed relative to the necessity of the antipernicious anemia principle for normal erythropoiesis in the fetus. The possibility is considered that the antipernicious anemia principle is not necessary for normal erythropoiesis in the fetus.

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THE LIVER IN PELLAGRA.

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THE possible relation of disturbed liver function to the clinical syndrome of pellagra occasionally has been suggested,^{3,11,22-24} and the common occurrence of fatty infiltration of the liver in patients dying of pellagra has been noted by all students of the disease. It is admitted that anatomic change in the liver cannot be correlated with dysfunction and that it is entirely possible that the same nutritional defect causing the clinical picture of pellagra may produce the hepatic changes found postmortem.²⁴ There is experimental evidence to suggest that the factor active in causing mucosal lesions in pellagra may be different from that resulting in fatty liver,¹⁷⁻¹⁹ but there is no record of similar observations in human disease. The discovery by Elvehjem and his associates⁷ that nicotinic acid is the specifically deficient substance in uncomplicated blacktongue of dogs has been widely applied to the treatment of human pellagra with almost uniformly satisfactory results. The fact that nicotinic acid was isolated from liver extract by Elvehjem *et al.* has led to the assumption that all liver extracts are rich in this substance and to the widely prevalent idea that the beneficial effects of liver and liver extracts in pellagra are due to nicotinic acid alone. These conclusions seem open to question. It seems quite certain that liver substance and liver extracts prepared for oral use are rich in nicotinic acid or its amide but the method of preparation of the fractions for parenteral use precludes the presence of these substances in large amounts. Nicotinic acid is about as soluble in 95% alcohol as in water and the final precipitation of the "fraction G of Cohn" from 95% alcohol probably leaves most of the acid originally present in liver in the supernatant fluid. Unfortunately, no adequate method has yet been devised for the assay of nicotinic acid in liver extracts. Since Goldberger and Sebrell⁸ reported the curative action of liver extract in blacktongue of dogs, numerous observers have recorded its great efficacy in pellagra.^{12,14,20} Our own experience has been that no substance so far tried is as rapidly

curative for all manifestations of pellagra as the Cohn fraction for intravenous use²⁵ and it is not possible to demonstrate the presence of free nicotinic acid in this substance,^{4,26} though nicotinamide may be present in small amounts. We have not failed to observe marked improvement in all manifestations of pellagra within 24 hours of its administration intravenously in amounts varying from 20 to 80 cc. In this respect, our experience has varied markedly from that of Ruffin and Smith¹⁴ but has been constant in a considerable number of instances. The efficacy of such a highly refined liver extract is the more interesting since Miller and Rhoads,¹⁰ using rats as test animals, found that refined liver extracts whether fed or injected were apparently deficient in "vitamin B2G." In our experiments, 1 patient was not improved by the prolonged intravenous administration of presumably adequate amounts of nicotinic acid (Case 1, Experiment 2, this report) but was apparently cured by a single injection of commercial liver extract prepared for intravenous use.

It has seemed to us that important information might be gained by testing the pellagra-curative action of the "G fraction" derived from the liver of an untreated pellagrin. Many authors have drawn analogies between pernicious anemia and pellagra and to be complete, such an experiment should include the use of the pellagrous liver extract in the treatment of pernicious anemia. Corollaries of this experiment have already been carried out. Spies and Payne²¹ and Saleh¹⁵ have shown that achlorhydric gastric juice of pellagrins contains the intrinsic factor of Castle; these observations we have confirmed. Richter, Ivy and Kim,¹³ Wilkinson and Klein,²⁷ and Goldhamer, Isaacs and Sturgis⁹ have demonstrated that the livers of untreated patients with pernicious anemia may be lacking in the antianemic factor and suggested that it may be a storage substance rather than an inherent constituent of liver. Schiff, Rich and Simon¹⁶ showed that some antianemic substance may remain in severely damaged livers but the weight of evidence would indicate that in pernicious anemia there is failure of storage of the antianemic substance.

Recently there has been opportunity to test the antianemic and antipellagric potency of a pellagrous liver, control studies with extract of a normal human liver have not been carried out.

Materials. Human liver extract was prepared by the method of Cohn⁵ for intravenous administration. The product was a clear, dark amber solution, sterile in aerobic and anaerobic cultures and non-toxic for rabbits in doses of 5 cc. per kilo, 25 cc. represented 100 gm. of the original liver.*

Source of pellagrous liver extract: G.D. (No. 120294) was admitted to the University Hospital, April 25, 1938, complaining of diarrhea with 20

* Commercial liver extract was purchased from Parke, Davis & Co. in ampules containing 20 cc., representing 100 gm. of mammalian liver. Nicotinic acid used for intravenous administration was the crystalline product purchased from the Eastman Kodak Company; Coramine was furnished by the Ciba Company.

to 30 stools daily, nausea, vomiting, abdominal pain, soreness of the mouth and tongue and of an eruption on the hands, feet and perineum; all of about 3 weeks' duration. There was a history of anorexia over a period of about 7 months though adequate food was available.

The patient was a negro woman aged 35, remarkably emaciated and dehydrated. Weight, 80 pounds; temp., 103° F.; pulse, 140; resp., 26; blood pressure, 88/60. There was ulcerating and bullous dermatitis of the neck, face, forearms, perineum and intercrural regions, ankles and feet, the elbows and knees showed thickening and pigmentation of the skin. The tongue was fiery red with absence of papillæ and severe ulceration of the inferior surface, the buccal mucosa was red and ulcerated. There was impaired resonance and many crackling râles at both lung bases, the heart was small and there were systolic murmurs at the apex and pulmonic area. The abdomen was distended and generally tender. There were no abnormal neurologic findings. The genitalia gaped and there was a profuse foul seropurulent vaginal discharge. The blood contained 5.5 gm. % of hemoglobin, 1,880,000 R.B.C., 5250 W.B.C.; blood sugar was 80 mg. %, non-protein nitrogen, 22.4 mg. %. Wassermann and Kahn tests were strongly positive. The urine contained albumin and casts, pus and large amounts of porphyrin. Blood cultures were sterile, stool cultures negative for organisms of the typhoid-dysentery group.

This woman was given stimulation and active measures for hydration were employed, no specific therapy for pellagra was used. She died, suddenly and unexpectedly, some 7 hours after admission. Necropsy was done 5 hours after death; in addition to severe superficial lesions of pellagra there were early bronchopneumonia, atrophy and superficial ulceration of the gastric and intestinal mucosa, fatty infiltration of the liver and rectal lesions of granuloma venereum. The liver weighed 1260 gm.; 760 gm. after being freed from connective tissue, blood-vessels and bile ducts, was taken for extraction. The method of Cohn was followed in detail, the extract which has been briefly described and which contained no demonstrable nicotinic acid or nicotinamide⁴ was used in the following experiments.

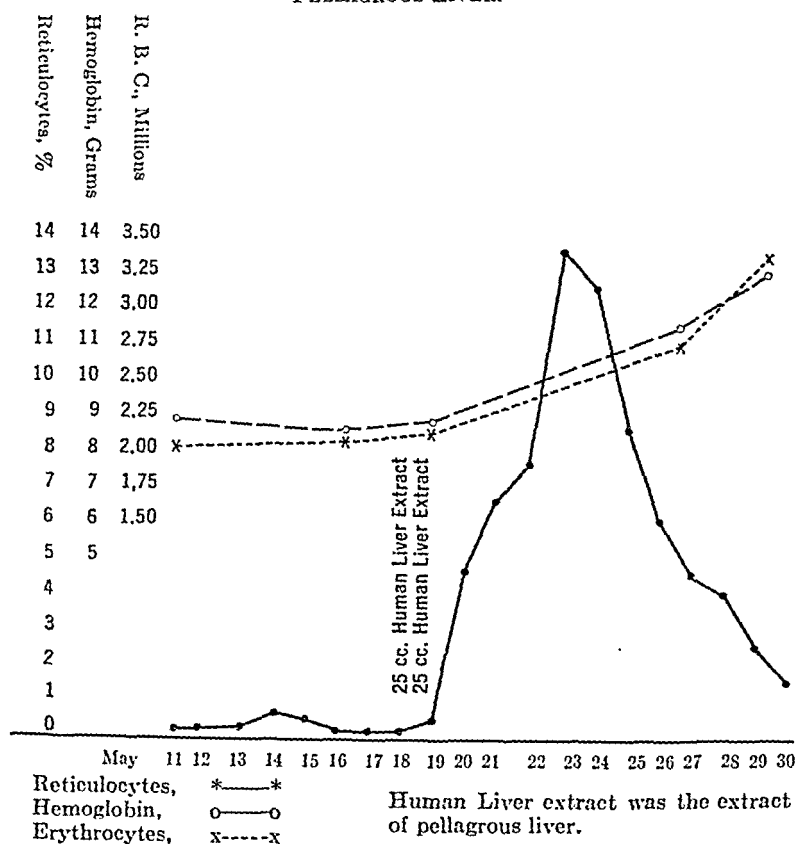
Method. Patients subjected to experiment were given complete physical and special neurologic examination. Quantitative, morphologic and chemical examinations of the blood were carried out in detail. Gastric analyses after histamine were made on the morning after admission and at weekly intervals. The urine was tested for all abnormal constituents including porphyrins. The stools were examined microscopically and by culture. Roentgen ray examinations of the thorax and gastro-intestinal tract were complete. The cerebrospinal fluid was secured and all usual tests done. Electrocardiograms were made on admission and at weekly intervals. Colored photographs were made of the tongues of the patients with pellagra before and after various therapeutic measures. Patients were kept at rest in bed, the woman with pernicious anemia was given regular ward diet, the subjects with pellagra were held on pellagra-producing diet. Reticulocytosis was used as the index of stimulation of hematopoiesis in the case of pernicious anemia. In the subjects with pellagra, qualitative tests for porphyrin were done on morning specimens of urine as the only objective indication of improvement aside from clinical estimation of symptoms and signs.^{1,2,6,22,25}

Experiment 1. Administration of extract of pellagrous liver to a patient with pernicious anemia.

CASE 1.—N. B. (No. 120643), a white woman, aged 45, was admitted to this hospital on May 11, 1938, complaining of weakness, loss of appetite and of inability to walk, all symptoms were of gradual onset over a period of about a year. She was a small, fairly well nourished woman, pale with

a striking lemon yellow color; there was slight general edema. Temp., 98.6° F.; pulse, 84; resp., 20; blood pressure, 128/90. The hair was dry and gray, the tongue liver-colored with total absence of papillae. The lungs showed nothing abnormal, the heart was small with systolic murmurs at apex and base. No abnormal findings were noted in the abdomen or genitalia. There were the signs of advanced combined sclerosis. The blood contained 8.8 gm. % of hemoglobin, 2,020,000 R.B.C., 7300 W.B.C.; smears showed marked macrocytosis, anisocytosis and poikilocytosis, occasional megaloblasts were seen. The volume of packed red cells was 26 cc. %: volume index, 1.38; color index, 1.4. Blood chemical determinations were

CHART 1.—RESPONSE OF ADDISONIAN ANEMIA TO EXTRACT OF PELLAGROUS LIVER.



not abnormal. The urine contained no albumin or sugar, urobilinogen was present. The gastric contents after histamine showed 0 free HCl, 5 degrees total acidity. The stools were not abnormal. Roentgenologic examination of the thorax and gastro-intestinal tract showed nothing unusual. Electrocardiograms were normal. Reticulocyte counts were done daily and are shown graphically in Chart 1, complete examinations of the blood were carried out at appropriate intervals. On May 18 and 19, extract of pellagrous liver was administered intravenously, 25 cc. each day. Reticulocyte response was prompt and satisfactory, reaching 13.2% on the fourth day and there was subsequent increase in the red cell count and hemoglobin. It seemed evident that extract of pellagrous liver was not lacking in the hematopoietic factor.

Experiment 2. Administration of extract of pellagrous liver to patients with endemic pellagra.

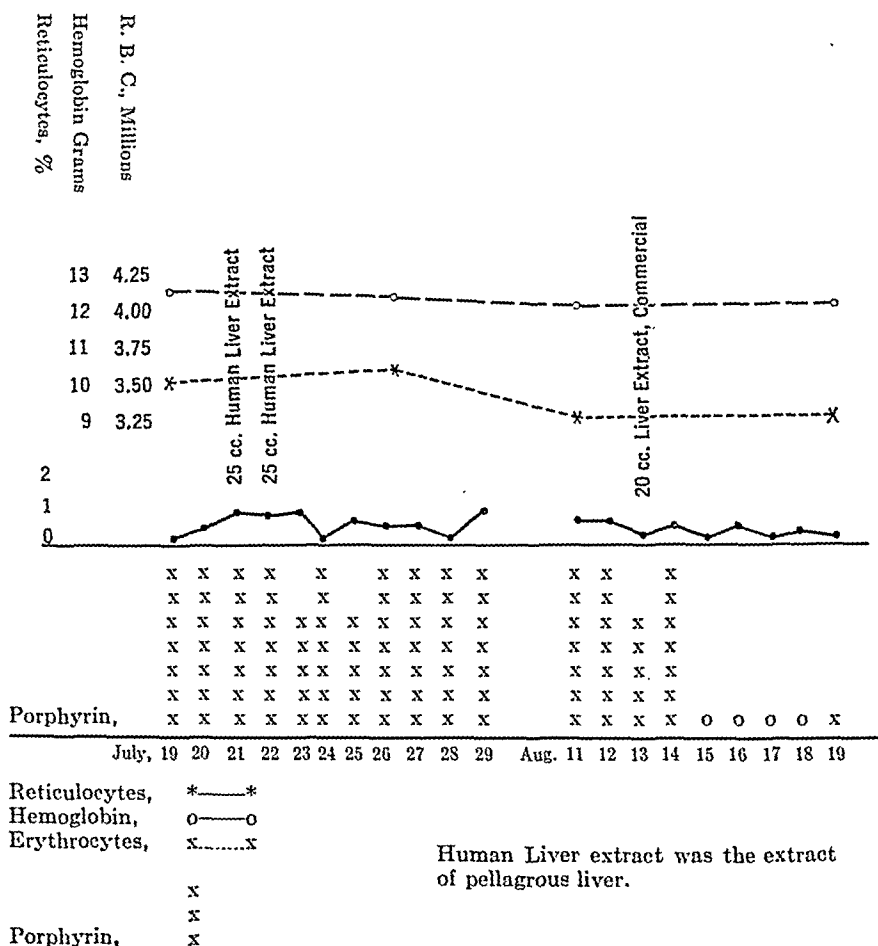
CASE 2.—L. H. (No. 121949), a white woman, aged 67, was admitted to this hospital, July 4, 1938. She was emaciated, pale, dehydrated and stuporous. There was slight desquamating dermatitis of the hands and forearms, the tongue was intensely red and slick at the tip and edges, vaginitis was moderately severe. Temperature was 103° F; pulse, 116; resp., 24; B.P., 130/90. Physical examination showed advanced arteriosclerosis and moderate cardiac enlargement. The blood contained 12.5 gm. % of hemoglobin, 3,500,000 R.B.C., 15,000 W.B.C.; the volume of packed red cells was 37 cc. %, color and volume indices were approximately 1. Non-protein nitrogen was 40 mg. %; other chemical and serologic examinations of the blood were not significant. The urine was concentrated and contained traces of albumin, many hyaline and granular casts and large amounts of porphyrin. The phenolsulphonephthalein output was 40%. The gastric contents showed 0 free HCl, 12 degrees total acidity. The cerebrospinal fluid was normal. Roentgen ray examination of the thorax and gastro-intestinal tract showed nothing unusual.

This patient was placed on soft ward diet which was very poorly eaten, large amounts of fluid were given orally and parenterally with slight improvement in the mental state and rapid reduction of the non-protein nitrogen content of the blood. On July 11, pellagra-producing diet was given and poorly taken; she rapidly became worse with increasing delirium and glossitis. From July 15 to 19, coramine was given hypodermically, 12 cc. daily, there was slight improvement in glossitis but porphyrinuria was not affected and delirium was not lessened. By July 21, the tongue was again fiery red. On July 22 and 23, the extract of pellagrous human liver was given, 25 cc. intravenously on each day; there was no effect on glossitis, mental symptoms or porphyrinuria, the reticulocytes were not increased. From July 26 to 30, nicotinic acid was administered intravenously, 75 mg. daily, with no improvement; on July 31, the dose was increased to 100 mg. and this amount was given until August 6, without clinical improvement or lessening of porphyrin in the urine. During this period and the ensuing week the patient was severely ill, food and fluids were given by nasal tube, a liquid diet with minimal pellagra curative constituents being used and parenteral administration of glucose and physiologic saline was almost continuous. On August 13, 20 cc. of commercial liver extract was given intravenously. Improvement was dramatic in its promptness and completeness. On the following day, the patient was quiet and coöperative, the tongue was pink and showed regeneration of papillæ on denuded areas, porphyrinuria remained maximal. On August 15, she was alert and asked for food, the tongue looked normal and porphyrinuria was absent. She continued to improve and on August 20 soft pellagra curative diet without yeast was given. Small amounts of porphyrin reappeared in the urine on August 18 and persisted, but clinical cure persisted and the patient was discharged clinically well on September 1, 1938.

CASE 3.—F. P. (No. 123481), a white man, aged 45, was admitted to this hospital, September 6, 1938. (It was his third admission for pellagra in 2 years. In July, 1938, he was apparently cured by nicotinic acid and was dismissed clinically well on July 31.) He was still well nourished but severely depressed. There was slight pellagrous dermatitis of the face and neck, with severe ulcerating bullous dermatitis of the hands and forearms. The tongue was slightly red and atrophic at the tip and edges, the buccal mucosa was pink and there were no genital lesions. Temperature was 99° F.; pulse, 100; resp., 18; blood pressure, 118/70. General physical and neurologic examinations were negative. The blood contained 10.5 gm. %

of hemoglobin, 3,800,000 R.B.C., 18,000 W.B.C.; the volume of packed erythrocytes was 32 cc. %, color index was 0.9, volume index, 1. Chemical and serologic examinations of the blood were not significant. The urine was scanty and highly concentrated, much porphyrin was present. The gastric contents showed 0 free HCl, 8 degrees total acidity. The cerebrospinal fluid was normal. Roentgenologic examinations of the thorax and gastro-intestinal tract were negative.

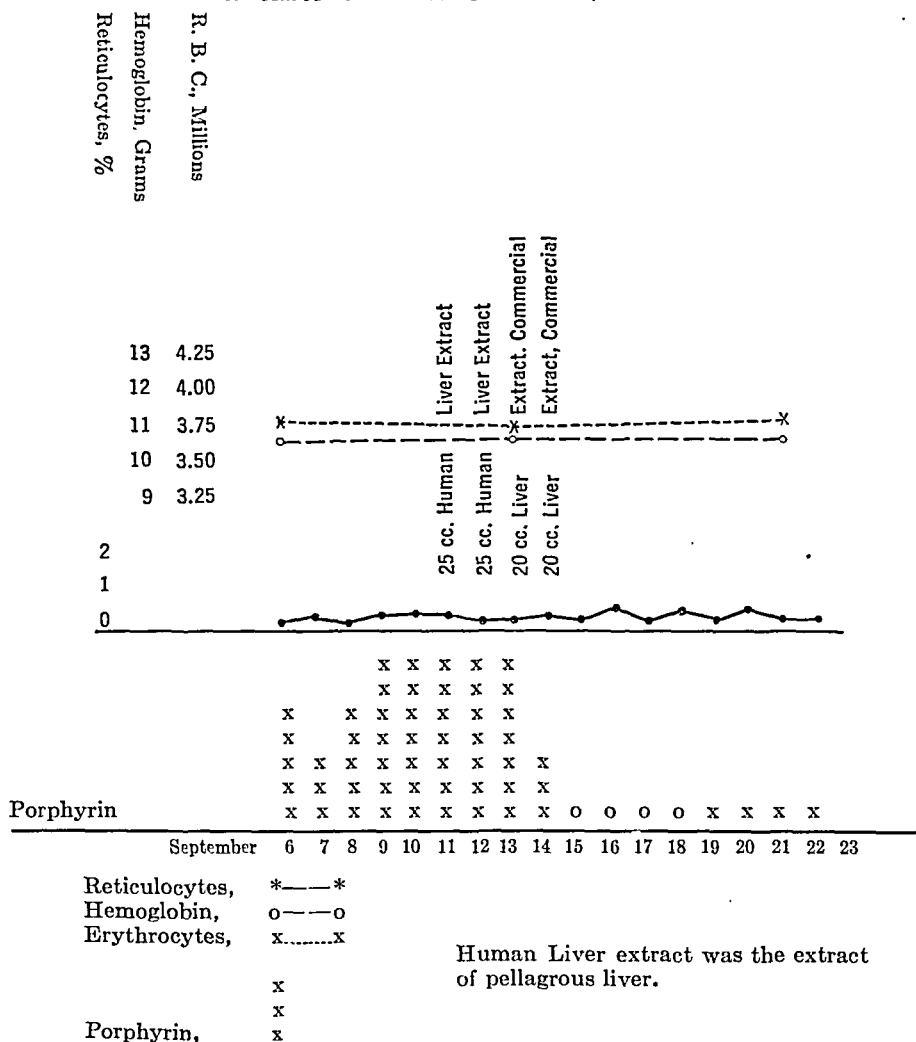
CHART 2.—EFFECT OF EXTRACT OF PELLAGROUS LIVER AND OF COMMERCIAL LIVER EXTRACT IN PELLAGRA. CASE 1, EXPERIMENT 2.



This man was placed on the glucose and water regimen of Spies, his total daily intake being 440 gm. of glucose and 3000 cc. of water, given orally and parenterally. Severe glossitis developed on September 9 and by September 11 the tongue was fiery red, totally denuded of papillae and severely ulcerated, the buccal mucosa was similarly red and ulcerated, nothing was taken by mouth. There was dusky erythema of the legs and a bullous eruption appeared on both ankles. Extract of liver was given intravenously, 25 cc. on this and the following day. There was no sign of improvement, glossitis and stomatitis became worse, an alveolar abscess developed about the first right lower molar tooth which

necessitated extraction. The man was semistuporous, temperature was 101° F. and porphyrinuria was extreme. The patient's condition seemed so urgent that further delay in treatment could not be justified. On September 13 and 14, 20 cc. of commercial liver extract was given intravenously. On the morning of September 14 the mental state was much improved, the tongue was pink as was the buccal mucosa and there was marked healing of the ulcers, porphyrinuria was much diminished. By the next day the patient was alert, coöperative and demanded food. The

CHART 3.—EFFECT OF EXTRACT OF PELLAGROUS LIVER AND OF COMMERCIAL LIVER EXTRACT IN PELLAGRA. CASE 2, EXPERIMENT 2.



tongue was of normal color and texture though small ulcers on the under surface has not yet healed, the buccal mucosa looked normal and dermatitis was much improved, porphyrin was absent from the urine. On the following morning (September 15), no oral lesions remained, the man sat up and read, and he was given solid pellagra curative diet, without yeast. Without further treatment he has continued to improve and has remained clinically well. Small amounts of porphyrin appeared in the urine on September 17 and have persisted.

Summary and Conclusions. Because failure of liver function or of liver storage of an essential substance has been suspected as a factor in the production of pellagra and since analogies have been drawn between pellagra and pernicious anemia, it seemed important to test the efficacy of an extract of pellagrous liver in the two diseases. Such an experiment seemed more significant since the commercial preparations containing the "fraction G of Cohn" are rapidly curative of both conditions.

It has been possible to secure the liver of a patient dying of severe untreated pellagra and to prepare an extract by the method of Cohn, which was suitable for intravenous administration. This extract has been given to 1 patient with typical pernicious anemia and to 2 patients with endemic pellagra. The amounts used represented in each instance 200 gm. of the fresh liver.

The patient with pernicious anemia showed a prompt and satisfactory reticulocyte response with subsequent increase in erythrocytes and hemoglobin. The individuals with pellagra showed no evidence of improvement and were later brought into good remission by the intravenous administration of a commercial liver extract.

The extract of a pellagrin's liver was rich in the hemopoietic factor but seemingly totally lacking in the pellagra curative substance present in commercial liver extracts. This would indicate the entire autonomy of the factors effective in the cure of pernicious anemia and pellagra.

No satisfactory method has been devised for the assay of nicotinic acid in liver extracts, but the method of preparation of such extracts for intravenous use makes it unlikely that significant amounts of the acid or its amide remain.

The experiments reported suggest the existence of a factor other than nicotinic acid, active in the cure of pellagra, which is present in normal mammalian liver and its refined extracts but absent from the liver of pellagra.

Since this report was submitted it has become evident that the substance in the urine recorded as "porphyrin" was not porphyrin but the unidentified chromogenic material isolated by Watson. It has been shown to have no constant relation to the amount of coproporphyrin in the urine but is a rough index of the degree of nutritional disturbance shown by the patient.

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ACHLORHYDRIA IN THE LEUKEMIAS.*

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DURING the past 4 years, 20 cases of myelogenous and lymphatic leukemia have been studied for the following purposes: 1, to investigate the incidence of true achlorhydria in leukemia, 2, to convass the old concept of leukanemia of Leube in the light of Castle's conditioned deficiency hypothesis as follows: *a*, to find out if a pernicious type of anemia occurs in association with leukemia (*i. e.*, macrocytic anemia with glossitis, achlorhydria, and neurologic disturbances); *b*, to investigate the influence of liver extract therapy on such manifestations.

The alcohol test meal was used, and histamine given if free acid was absent after the first hour. Tongue prints were made according to the method of Middleton.

Frequent blood studies were performed during various phases of relapse and remission under Roentgen-ray therapy. To each of the patients exhibiting achlorhydria with severe anemia (5 in all) was administered an adequate course of parenteral liver therapy and the reticulocyte response was noted.

Three of these exhibited macrocytic anemia and 2 microcytic. In no case was there any significant reticulocyte response to liver

* This study was aided by a grant to the Hematological Fund from Mrs. Bruce Ford.

therapy. Smooth tongue was found in 8 cases (40%). Achlorhydria was present in 7 cases (35%). There was no correlation between achlorhydria and smooth tongue. The amount of prior Roentgen-

CHART 1.—SIGNIFICANT DATA IN 20 CASES OF LEUKEMIA.

Patient.	Age.	Sex.	Diagnosis.	Known duration of disease.	Tongue.	Gastric analysis.	C. B. C. during exacerbation	Macrocytosis.	Intermittent prior x-ray therapy.
J. C.	53	M.	A.M.L.*	1 mo.	Smooth	No free HCl	Hb 38% RBC 2.2 WBC 29,000	+	No.
J. D.	61	M	C. L. L.*	1 yr.	Normal	No free HCl	Hb 31% RBC 1.5 WBC 210,000	0	2 mos.
L. E.	39	M	C. M. L.*	10 yrs.	Normal	Free HCl	Hb 40% RBC 2.4 WBC 23,300	0	7 yrs.
A. G.	38	M	C. M. L.	2 yrs.	Smooth	Free HCl	Hb 74% RBC 4.0 WBC 187,000	0	2 yrs
R. H.	38	F	C. M. L.	3 yrs.	Normal	Free HCl	Hb 50% RBC 3.1 WBC 120,000	0	3 yrs.
W. H.	47	M	C. M. L.	1 yr.	Normal	Free HCl	Hb 28% RBC 1.4 WBC 130,000	0	1 yr.
M. H.	44	F	C. M. L.	2 yrs.	Normal	Free HCl	Hb 55% RBC 3.5 WBC 230,000	0	2 yrs.
M. K.	42	F	A. M. L.	3 mos.	Normal	Free HCl	Hb 49% RBC 3.2 WBC 41,000	0	No.
L. L.	39	M	C. L. L.	2 yrs.	Normal	No free HCl	Hb 90% RBC 4.4 WBC 15,000	0	No.
F. M.	40	M	C. M. L.	4 yrs.	Normal	Free HCl	Hb 50% RBC 2.8 WBC 380,000	0	No.
M. M.	61	F	C. L. L.	3 mos.	Smooth	No free HCl	Hb 92% RBC 5.7 WBC 246,000	+	No.
C. N.	58	F	C. M. L.	1 yr.	Few papillæ	Free HCl	Hb 70% RBC 4.0 WBC 56,000	+	1 yr.
S. S.	46	M	C. M. L.	1 wk.	Few papillæ	No free HCl	Hb 57% RBC 3.7 WBC 86,000	0	No.
S. S.	34	M	C. M. L.	2 mos.	Few papillæ	Free HCl	Hb 46% RBC 2.8 WBC 49,000	0	No.
H. T.	59	M	C. M. L.	2 yrs.	Smooth	Free HCl	Hb 45% RBC 2.6 WBC 304,000	0	2 yrs.
E. V.	49	M	C. L. L.	6 mos.	Smooth	No free HCl	Hb 80% RBC 4.1 WBC 14,000	0	1 mo.
F. W.	54	F	C. M. L.	2 yrs.	Few papillæ	No free HCl	Hb 34% RBC 24 WBC 280,000	0	2 yrs
G. W.	39	M	C. M. L.	4 yrs.	Smooth	Free HCl	Hb 62% RBC 4.0 WBC 340,000	0	3 yrs
F. S.	58	F	C. M. L.	5 yrs.	Smooth	Free HCl	Hb 40% RBC 2.0 WBC 400,000	0	5 yrs.
S. K.	65	F	C. L. L.	3 mos.	Smooth	Free HCl	Hb 92% RBC 4.8 WBC 31,000	0	No.

* A. M. L. = Acute myelogenous leukemia.
C. M. L. = Chronic myelogenous leukemia.
C. L. L. = Chronic lymphatic leukemia.

ray therapy was likewise without influence on achlorhydria in this series. There was no correlation between achlorhydria and severe anemia, but of the 3 cases exhibiting macrocytosis, 2 were achlorhydric. Only 1 patient in this group presented neurologic disturbance and this was a rather inconclusive paraesthesia. This patient also complained of sore tongue.

There were 6 necropsies in this series (13 known to have died). Leukemic infiltration of the liver was found in all cases, but infiltration of the stomach was observed in only 1 (G. W.), and this patient had normal gastric acidity during life.

Chart 1 summarizes the pertinent findings.

Chart 2 compares the incidence of achlorhydria in this series with the expected frequency in a group of normal individuals from the data of Bloomfield and Polland.¹

CHART 2.—INCIDENCE OF ANACIDITY IN 20 CASES OF LEUKEMIA COMPARED WITH EXPECTED INCIDENCE OF ANACIDITY IN IDENTICAL AGE GROUPS OF NORMAL SUBJECTS.

Age.	Sex.	No. cases of leukemia with anacidity.	% Anacidity in leukemia in different age-groups.	Expected incidence anacidity (Bloomfield and Polland), (per cent).
30-39	M	1	16.6	3.5
40-49	M	2	20	10
50-59	F	2	40	25
60-69	M	1	100	31.7
	F	1	50	21.9

Although the number of cases is too small for statistical analyses, it may be significant that in each age group in both male and female subjects, achlorhydria in leukemia exceeds the "normal" incidence.

In recent medical literature, there is only one reported systematic study of the gastric secretion in leukemia.

Dobruff² summarizes his findings in 34 cases of myelogenous and lymphatic leukemia as follows: Anacidity occurred in more than one-half of the cases of myelogenous leukemia and in less than one-fourth of the cases of lymphatic leukemia. The results in our series do not indicate this type difference.

In 1900, Leube applied the designation "Leukanemia" to a group of patients presenting evidence of a combination of leukemia and severe anemia of pernicious type. The data here presented suggest that there is no reality in the concept, although it is admitted that leukemic infiltration of the stomach might conceivably destroy the intrinsic factor, and leukemic infiltration of the liver might conceivably interfere with storage of the "interaction products."

Recently Rich and Schiff³ reported a case of combined lymphatic leukemia and pernicious anemia in which both diagnoses were fully substantiated. Our experience is in agreement with the conclusion of these authors, that the existence of both diseases in the same individual is a coincidence.

Conclusions. 1. Although too small for accurate statistical analysis, this series of 20 cases of leukemia exhibits an incidence of achlorhydria (35%) which is higher than the expected "normal."

2. There is no correlation between achlorhydria, glossitis, anemia, and neurologic disturbances in this group.

3. Potent liver therapy has no effect on the associated anemia of leukemia.

4. The concept of leukanemia (Leube) is without demonstrable basis and the term should be dropped.

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THE USE OF VITAMIN B₁ IN REST PAIN OF ISCHEMIC ORIGIN.

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IN spite of newer methods of treating peripheral vascular disease, there are still patients who are unable to obtain relief from pain. This is especially true of that group of patients classified as having ischemic neuritis.

Because the problem of ischemia appeared to be basically that of a block in transportation of elements necessary for proper nutrition of tissues we attempted to decrease pain by supplying tissues deficient in blood with at least one of the essential elements, the absence of which is known to cause pain, namely vitamin B₁. The theory was that by injecting huge quantities of vitamin B₁ into the blood stream we might be able to raise the blood concentration of vitamin B₁ to such a level that even the reduced blood supply in ischemic areas could maintain an adequate vitamin B₁ content in such tissues.

Vitamin B₁ was chosen because it is essential for tissue metabolism (Peters⁷) and because it is known that its absence causes disturbance of nerve function resulting in pain. Vitamin B₁ is available in crystalline form and we have found that it can be given intravenously in huge doses with apparent safety.

Patients with ischemic neuritis seemed well suited to test the hypothesis that ischemic pain might be relieved by increasing the concentration of vitamin B₁ in the ischemic tissue. The pain in ischemic neuritis is sharp and burning, coming on in paroxysms or present constantly. Neurologic changes are present in some patients and absent in others. The term ischemic neuritis has usually been reserved for a type of rest pain which is present in patients with

extensive arterial occlusion without open lesions (Goldsmith and Brown³). We have had to broaden this concept, as it seems logical to assume that in arterial occlusion, whether it be as large as a femoral or as small as a digital artery supplying a single toe, the nerve trunks, as well as the other tissues in the ischemic area are deficient in blood. Ischemic neuritis may therefore be present in patients with gangrene or ulcers on an ischemic basis. Barker¹ has reported extensive degenerative changes in the peripheral nerves of the extremities of patients with thromboangiitis obliterans.

We find that vitamin B₁ can relieve pain of ischemic origin; whether by correcting a local deficiency or not we cannot say. We have no proof that there is a deficiency of vitamin B₁ in ischemic tissue.

Method of Treatment. At the start of the investigation 10 mg. (3000 International Units) of crystalline vitamin B₁* (thiamine chloride) were given intravenously every other day for 4 weeks to 2 patients with ischemic neuritis with no influence on pain. The dose was then increased to 100 mg. (30,000 International Units) intravenously every other day. A patient (Case 1, Table 1) who had paroxysms of severe pain involving both legs, unrelieved by any other form of therapy, obtained no relief from 10 mg. of vitamin B₁ given intravenously twice a week for a month. Following the first injection of 100 mg. the pain subsided abruptly. From then on we used the large doses.

The method and amount of vitamin B₁ administered to each patient is given in Table 1. The intravenous route was used in all except Case 10, who received vitamin B₁ intramuscularly, and in Case 2 in which intravenous therapy was supplemented by some intramuscular injections. All patients, excepting Cases 3 and 10, received 100 mg. doses until pain was relieved. Vitamin B₁ was given daily, every other day or twice a week, depending upon the severity of the pain.

Type of Patient Treated. Ten patients have been treated with large doses of vitamin B₁. All had severe, prolonged symptoms—lasting from 1 month to 8 years—which had not responded to previous therapeutic measures (Table 1).† Nine of the patients (Cases 1 to 9) had ischemic neuritis. Three of these patients (Cases, 6, 7 and 9) had ulcers or gangrene. Case 10 had early thromboangiitis obliterans with pain probably due to arteriolitis. With the exception of Case 10, all had evidence of advanced arterial disease. Nerve crushing for relief of pain had been rejected by the surgeon in 3 patients (Cases 1, 4 and 7) because of fear that the incision would not heal and that ischemia might be present in part of a nerve trunk above a possible site of nerve crushing.

Two of the patients (Cases 1 and 2) had diabetes mellitus in addition to arteriosclerosis; 2 (Cases 6 and 10) had thromboangiitis obliterans. Five of the cases (Cases 1, 3, 4, 8 and 9) were treated as ambulatory patients; 4 (Cases 2, 6, 7 and 10) were admitted to the hospital and treated. Case 5 was treated at home.

* We are much indebted to Merck & Co. for their kindness in supplying the vitamin B₁ required for these studies.

† Cases 4 and 7 were patients at the Mount Sinai Hospital, Medical Service No. 2.

TABLE 1.—EFFECT OF VITAMIN B₁ ON ISCHEMIC REST PAIN.

Case, sex, age (yrs.).	Diagnosis.	Degree of peripheral vascular disease.	Type of pain.	Previous treatment.	Amount of vitamin B ₁ .	Effect on pain.	Remarks.
1 M 65	Arteriosclerosis Diabetes mellitus	No pulses below femoral arteries. Oscillometric readings zero at ankles, much reduced at thighs. Knee and ankle jerks absent. Hypertension over right femoral artery. Vibratory sense impaired. Reflex vasodilatation test indicative of advanced arterial occlusion.	Ischemic neuritis. Mod. pain 1932-1937; then severe pain for 13 mos. Paroxysms of sharp, burning pain, worse over right lower half each leg. Intermittent claudication at a quarter block. Pain stopped sleep.	Bed rest, suction and pressure, tissue extr., alc. in subarachnoid space, methyl-D-acetyl choline iontophoresis, hypert. saline intraven. sedatives, conc. yeast extract, sod. chl. orally.	100 mg. every other day for 5 doses; 25 mg. once a week for 2 doses; 50 mg. once a week for 5 doses; no B ₁ for 2 mos.; 100 mg. started again and given daily for 1 wk.; 3 times a week thereafter for 2 wks.	Relief of pain for 1st time following 1st injection of 100 mg. Much impr. for 10 wks. Pain returned on stopping B ₁ and increased for 2 mos. B ₁ started again after lapse of 2 mos. After 1 wk. pain was less; after 2 wks., definitely impr.; after 3 wks. B ₁ edema of feet developed and severe pain recurred. B ₁ stopped.	Relief of pain 1st time in 13 mos. with start of large doses of B ₁ . Contd. at work and smoked. Bed-rest and other estab. methods of treatment should be used with B ₁ therapy. Neurol. signs unchanged.
2 F 65	Arteriosclerosis Diabetes mellitus	No pulses below femoral arteries. Oscillometric readings zero at ankles. Vibratory sense impaired.	Isch. neur. 10 mos. without relief. Severe rest pain and intermittent claudication. Constant ache in both feet with paresthesias and numbness in toes. Pain stopped sleep.	Bed rest, hypertonic saline intravenously, histamine iontophoresis, diathermy.	100 mg. twice a wk. for 3 wks.; no B ₁ for 1 mo.; 3 doses of 100 mg. in 4 days.	Complete relief of pain in 3 wks. Much relief after 1st injection. After stopping B ₁ , began to have mod. pain 1 mo. later. Paresthesias and numbness of both feet. B ₁ again relieved pain.	Relief of pain 1st time in 10 mos. Return of pain when B ₁ was stopped. Relief again with B ₁ . Neurol. signs unchanged.
3 M 51	Arteriosclerosis Hypertension Hemiplegia 2 years ago	Dorsalis pedis pulses weak—circulation in feet otherwise good. Type of pain and advanced sclerosis elsewhere suggested diagnosis of ischemia of peripheral nerves, somewhere along course from cord.	Isch. neur. 4 yrs. Burning pain in soles of feet radiating up legs. Coldness and numbness of both feet.	Bed rest, tissue extr., suction, and pressure, diathermy, removal of foci of infection.	20 mg. every other day; B ₁ stopped after 2 mos. and conc. yeast extr. given by mouth; 20 mg. B ₁ intraven. started again every other day.	Compl. relief of pain in 2 wks. On stopping intravenous B ₁ pain grad. ret.; after 4 mos. was severe. Pain relieved compl. in 12 days after resuming B ₁ intravenously.	Pain of ischemic neuritis unrelvd. for 4 yrs. responded to vitamin B ₁ . Pain relvd. 2 mos. after stopping B ₁ . Relieved again by B ₁ intrav.
1 M 67	Arteriosclerosis Hemiplegia	No pulses in either foot. Believed to have ischemia somewhere along course of peripheral nerve.	Isch. neur. 8 yrs. Burning pain in sole of right foot. Unable to sleep.	Bed rest, suction and pressure, tissue extr., baking, massage, diathermy, sedatives, salicylates, yeast tablets, calc. gluconate.	100 mg.—3 doses in 1 wk.; 2 cc. physiol. saline, 2 injections.	For 1st time in 8 yrs. had less pain in rt. foot after 1st injection. After 3d injection pain only slight. Pain relvd. with intensity within 10 days after stopping B ₁ .	Persistent form of pain unrelvd. any time over a pd. of 8 yrs was relvd. for 1st time by B ₁ .

5	F	75	Bilateral popliteal embolism. Arteriosclerosis.	No pulses below femoral arteries. Oscillometric readings zero below knees.	Isch. neur. Severe, burning pain in both legs, 1 mo. Unable to sleep because of pain.	Bed rest, sedatives and heat to legs.	100 mg. every other day for 3 doses.	Less pain after 1st injection. No pain after 3d injection. Return of pain 2 wks. after stopping B ₁ .	Relief of pain of ischemia following embolism.
6	M	63	Arteriosclerosis. Acute thrombosis of femoral artery, gangrene of foot	No pulses below femoral in right leg. Line of demarcation at mid-leg on right and superficial ulceration lower half of leg. No pulses in left foot.	Isch. neur. in massive occlusion. Constant, burning pain in right foot and lower third of leg for 1 mo. Unable to sleep because of pain.	Bed rest and sedatives.	100 mg. daily for 3 days.	Very little pain following 2d injection. Leg amputated wk. later.	B ₁ tried in a case of massive ischemia with gangrene. Pain relieved.
7	M	57	Arteriosclerosis. Femoral thrombosis	No pulse in right femoral artery. Rubor of right extremity up to mid-leg. Admitted for conservative treatment for 2 weeks but advised that amputation would probably be necessary.	Isch. neur. in an extremity with a massive occlusion. Severe pain, preventing sleep for 5 mos.	Bed rest, suction and pressure and sedatives.	100 mg. daily for 7 days.	Less pain following 3 injections and practically no pain after 5th dose of B ₁ .	Pain of massive ischemia relieved. Nerve crushing rejected for fear incision would not heal. Amputation advised for necrosis of toe.
8	M	78	Arteriosclerosis	No pulses in either foot. Cyanosis of right 4th and 5th toes, rubor of other toes. Partial occlusion of left axillary artery.	Isch. neur. in extremity with popliteal thrombosis. Constant burning pain in toes of right foot present for 3 yrs., continuous for 3 mos. Unable to sleep 3 or 4 nights a week because of pain.	Bed rest, suction and pressure and sedatives.	1. 200 mg. in 2 days. 2. 2 cc. physiol. saline twice a wk. for 2 wks. 3. 100 mg. B ₁ . 4. No B ₁ .	1. Relief of pain after 1st injection of 100 mg.; able to sleep. 2. Pain grad. returned and became severe. Unable to sleep. 3. Definitely less pain. Able to sleep. 4. Pain returned in 1 wk.	Relief of pain appeared to be def. associated with B ₁ administration.
9	M	43	Thromboangitis obliterans	T.A.O. for 23 yrs. One toe remaining on right foot, 2 on left. Ulcer on right foot for 14 yrs. No pulse below femoral on right. Oscillometric readings at ankles minimal.	Constant, severe pain in ulcer on right foot, radiating up foot for past 3 mos. Pain up foot, prob. isch. neur. Moderate pain in toes of left foot on isch. basis.	Amputation of toes, sodium citrate intravenously.	1260 mg. in 31 days.	Following 2d injection no pain for 1st time in 3 mos. Severe pain some nights during mo. of treatment, but usually had little or none. At end of B ₁ therapy severe pain returned in 10 days.	Pain of ischemic neuritis relieved by B ₁ . Ulcer pain not completely relv'd. Pain in left foot relv'd. in 10 days.
10	M	32	Early thromboangitis obliterans	All pulses present. Evidence of slight claudication by ergometer test.	Burning pain in toes at intervals for 5 yrs. Pain in toes recurred 2 mos. ago with ache in lower leg. Pain may be due to arteriolitis.	Diathermy and sedatives.	50 mg. daily for 3 days; 100 mg. daily for 2 days; 50 mg. 3 times a wk. for 2 wks.	No relief of pain.	Patient with early thromboangitis obliterans with probable arteriolitis unrelieved by B ₁ .

Results. Administration of vitamin B₁ was followed by complete relief of pain within 1 day to 2 weeks in 7 patients (Cases 2 to 8). Cases 1 and 9 obtained partial relief of pain; Case 10, with early thromboangiitis obliterans, was the only one not benefited.

The relief of pain in these patients was striking. These were selected patients with severe pain who had been refractory to the usual forms of therapy. When vitamin B₁ was stopped, pain usually returned within 2 weeks but was again relieved by more vitamin B₁. One patient (Case 8) with a popliteal thrombosis and a cyanotic toe was almost completely relieved following the first injection of 100 mg. After 200 mg. had been given, physiologic saline was substituted: pain returned within 2 weeks and he was again unable to sleep. After another dose of 100 mg. of vitamin B₁ pain was definitely less and he was able to sleep. Another patient (Case 3) obtained relief of pain within 2 weeks for the first time in 4 years with 20 mg. of vitamin B₁ intravenously every other day. When vitamin B₁ was stopped by the intravenous route and given orally, pain gradually returned within 2 months. Resumption of intravenous administration of vitamin B₁ relieved pain completely within 12 days.

Case 7, with thrombosis of a femoral artery and beginning gangrene, had been in 2 other hospitals and had obtained no relief from constant intense pain. The surgeon advised mid-thigh amputation, rejecting nerve crushing for fear the incision would not heal. Prior to amputation he was given 100 mg. of vitamin B₁ intravenously daily. Within 3 days he was comfortable and after 4 injections he was able to sleep without any sedatives. Amputation was not prevented by vitamin B₁ in this patient, but the ability to relieve the pain of such patients makes therapy more elastic, so that pain *per se* need not be considered a factor in deciding about the advisability of amputation.

Pain recurred in 1 patient with ischemic neuritis while under treatment. This patient (Case 1) had extreme pain before therapy and the pain on recurrence was just as severe. Pain recurred when he developed edema of both ankles as a result of cardiac decompensation which may have contributed to the return of pain.

Neurologic changes (Cases 1, 2 and 6) were unaffected by vitamin B₁. This coincides with the experience of Spies and Aring,⁹ who relieved the peripheral neuritis of patients with pellagra with vitamin B₁ parenterally without improving the objective changes.

Three of the patients (Cases 6, 7 and 9) with ischemic neuritis also had ulcers. Case 7 was completely relieved, Case 6 had very little pain following vitamin B₁ therapy, and Case 9 was partially relieved. The ulcers were not improved by vitamin B₁.

The return of pain after discontinuance of vitamin B₁ is not unexpected since the original occlusive process is little changed.

Obviously vitamin B₁ therapy should not preclude methods designed to increase peripheral circulation.

Trial of Vitamin B₁ in Intermittent Claudication. The relief of rest pain in ischemia by vitamin B₁ suggested an experimental trial in ischemic muscle pain, namely intermittent claudication. Two patients with intermittent claudication were given daily intravenous injections of 100 mg. of vitamin B₁ for 8 days and then 100 mg. twice a week for a total of 1400 mg. in a period of 4 weeks.

Case A, a man of 48, with thromboangiitis obliterans, who had intermittent claudication at 2 to 3 blocks was unable to walk farther after receiving 1400 mg. of vitamin B₁. Testing with an electrical ergometer⁵ before and after vitamin B₁ revealed no change.

Case B, a man of 55, with peripheral arteriosclerosis and occlusion, had intermittent claudication at 1 block for 2 years. While receiving vitamin B₁ his walking distance gradually increased, until at the end of a month he was able to walk 5 to 8 blocks, fatigue being less intense than it had been at the end of a block prior to receiving vitamin B₁. In pacing tests, he was able to walk 480 steps instead of 90 before fatigue began. The ergometric records after 8 days of vitamin B₁ therapy disclosed no objective improvement, although pain during the second test was not as severe as it had been in the test performed before vitamin B₁ was given. Three weeks after discontinuance of vitamin B₁ the walking distance was reduced to 3 blocks and early fatigue was returning.

The results in these 2 patients are equivocal and these studies are being continued.

Vitamin B₁ in Experimental Ischemia. An attempt to determine whether these doses of vitamin B₁ injected into a normal individual influence the phenomena following experimental ischemia utilized an experiment described by Lewis, Pickering and Rothschild.⁶ Lewis *et al.* showed that pressure of 160 mm. Hg applied to the upper arm produces (1) ascending numbness and (2) anesthesia below the cuff. In every case numbness appeared within 13 to 16 minutes, anesthesia several minutes later. Both, they say, are caused by ischemia of nerve trunks lying immediately under the cuff; not to direct pressure on nerve. That numbness and anesthesia were not caused by ischemia distal to the cuff they proved by producing identical numbness and anesthesia by pressure over nerve trunks alone, maintaining normal blood flow to the arm.

We have reproduced this experiment for use before and after administering 100 mg. doses of vitamin B₁ intravenously. The rate of ascent of anesthesia was found to be more repeatable and more objective than that of numbness. All tests for anesthesia were made by means of one horse-hair.

In 3 of 4 experiments with vitamin B₁ the ascent of anesthesia was delayed. In 1 experiment, anesthesia reached the wrist in 21.8 minutes without vitamin B₁. The following day anesthesia

reached the wrist in 29 minutes, after 100 mg. of vitamin B₁ had been injected. A week later the experiment was repeated without vitamin B₁ and anesthesia reached the wrist within 22 minutes. In 1 of the 4 experiments, ascent of anesthesia was not delayed by vitamin B₁.

The results of these experiments were suggestive but equivocal.

Discussion. The use of vitamin B₁ in ischemic rest pain at present is on an empirical basis. Oral administration was discarded because of failure to influence pain in 2 patients. Ten milligrams intravenously likewise did not relieve pain and doses of 100 mg. intravenously were usually required. Williams and Spies¹² point out that the amounts of vitamin B₁ necessary to obtain the same therapeutic response by the intravenous, subcutaneous or oral routes are in the ratio of 1:6:40. Although the subcutaneous and oral routes are satisfactory in the great majority of patients with true vitamin B₁ deficiency, patients with ischemic pain are a special group with suspected local avitaminosis on an obstructive basis and require an unusual method of administration of vitamin B₁.

When using large amounts of vitamin B₁ parenterally it is at present necessary to estimate toxicity and the rate of its excretion. Rowlands and Wilkinson⁸ found the normal blood vitamin B₁ to be 6.5 to 16.5 microgm. per 100 cc. of whole blood. They showed that 4 mg. of vitamin B₁ injected intramuscularly raises the blood vitamin B₁ content within 15 minutes from 5 microgm. to 14 microgm. The blood vitamin B₁ fell to the original level within 1 hour. There is evidence in the literature that vitamin B₁ is non-toxic even in relatively large doses. Spies¹² has used doses of 500 mg. orally with no toxic effects. Weiss and Wilkins¹¹ have administered as much as 100 mg. intravenously without ill effects.

The only reference to pathologic changes observed from using curative amounts of vitamin B₁ found in the literature was that of Engel and Phillips² reporting liver damage in rats after their recovery from vitamin B₁ deficiency by administering 120 microgm. of crystalline vitamin B₁ per 100 gm. of ration. One-half milligram of vitamin B₁ injected into deficient rats produced similar changes in the liver. Steinberg¹⁰ has reported herpes zoster in patients who received doses of 2000 units (about 7 mg.) intravenously at weekly intervals, supplemented by 800 units (about 3 mg.) by mouth daily. Cowgill, in discussing a paper by Goodhart and Jolliffe,⁴ quotes Molitor as being able to kill mice, rats, rabbits and dogs with intravenous vitamin B₁ equivalent to giving 25,000 to 50,000 times the daily normal requirement. Carried over to the human species the lethal dose for man would be from 25,000 to 50,000 mg.

In our investigations, we observed no toxic effects. None of the patients had any symptoms following the injections with the exception of 1 (Case 6) who stated that slight, transitory vertigo followed 1 injection. There were no significant changes in the blood pres-

sure or heart rate of 6 patients following the intravenous injection of 100 mg. of vitamin B₁.

We have no information on the mechanism of relief of rest pain in ischemia by vitamin B₁ other than that local tissue metabolism may be temporarily improved as suggested by the work of Peters.⁷ Evidence is accumulating that the absence of vitamin B₁ does not cause nerve degeneration but probably disturbs the normal function of the nerve cell (Engel and Phillips² and Wintrobe, Mitchell and Kolb¹³). We do not know whether, in those patients relieved of ischemic pain by vitamin B₁, the vitamin B₁ concentration in the ischemic tissues had been depressed to a level sufficient to cause pain or whether pain was relieved by raising tissue concentration of vitamin B₁ to above a normal level. These large doses of vitamin B₁ failed to increase skin temperature in the toes, indicating that relief of pain resulted from something else than from increased blood flow. Vitamin B₁ may relieve pain in a manner unknown to us at present.

The use of vitamin B₁ must not lead to the neglect of measures to increase circulation. We have limited its use to selected patients with pain unrelieved by other measures.

Summary. 1. Vitamin B₁ was given intravenously in doses of 100 mg. to 10 patients with ischemic neuritis or rest pain of ischemic origin. Seven obtained complete relief of pain; 2 patients obtained partial relief and 1 failed to obtain any relief. Pain was relieved only as long as vitamin B₁ was administered parenterally. Maintenance amounts of vitamin B₁ (20 to 100 mg. once or twice a week) were required to keep patients free from pain as long as the vascular condition remained unchanged.

2. Gangrene, ulcers and objective neurologic changes were not improved by vitamin B₁.

3. Vitamin B₁ does not supplant the usual methods of treating peripheral vascular disease but is worthy of clinical trial in patients with refractory pain. Measures designed to increase peripheral circulation should always be used in these patients.

4. Vitamin B₁ was used intravenously in 2 patients with intermittent claudication and in normal individuals under conditions of experimental ischemia with equivocal results.

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THE DRUG TREATMENT OF ANGINA PECTORIS DUE TO CORONARY ARTERY DISEASE.

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FOUR years ago a clinic for patients with precordial pain was organized by us at the Mount Sinai Hospital for the study of angina pectoris due to coronary artery disease. We have been interested particularly in determining the efficacy of drug therapy in this disease, for innumerable remedies have been described and at present there is great difference of opinion concerning their value. The frequency of this disease emphasizes the importance of systematizing its therapy and of properly evaluating the agents used. A preliminary report has already been made by one of us.¹⁵

The difficulties of the problem have been insufficiently recognized by many writers, who have not considered the natural course of angina pectoris, which is capricious. Thus patients with angina pectoris frequently experience periods of spontaneous remission, during which improvement may be erroneously ascribed to any drug being taken at the time. Furthermore, attacks of pain may be induced by a variety of factors, and it is usually impossible to control all of these. The emotional status of these patients is of particular importance¹¹ and may actually determine the occurrence and degree of pain. It is necessary to take cognizance of all these factors and to exercise great caution in evaluating a drug.

The literature on the drug treatment of angina pectoris is very extensive but, since it has been well presented in numerous articles, will be entered into here only to point out the great variety of remedies advised. Heberden¹⁰ and Parry¹⁸ early recognized that morphine and whiskey relieved attacks and also suggested that they might prevent them. Recently several authors^{12, 14, 21} have emphasized good results with alcohol. Naturally such drugs should not be used for extended periods. The nitrites, having been found to relieve attacks of angina pectoris, have also been used to prevent attacks with supposed success.^{16, 19, 21} During the present century the xanthine derivatives have enjoyed preference in routine practice and good results have been reported in over 80% of cases.^{6, 17, 20}

It is noteworthy, however, that there has been little agreement among many writers concerning the relative merits of the various members of this group. Some have obtained better results with theobromine compounds, others with the theophylline group. Numerous other drugs, including tissue extracts,^{3,24} trichlorethylene,¹³ and so on, have been extolled for their relief of the anginal syndrome. In interpreting these results it should be pointed out that, as a rule, only the drug being studied was administered and the patient's symptoms during this period contrasted with those when the drug was withheld. We do not believe such a study to be sufficiently controlled to allow definite conclusions to be drawn. On the other hand, Evans and Hoyle,² employing a variety of drugs as well as a placebo, found that none was of specific value, for the degree of success with any one drug was no greater than with the placebo, although occasionally a drug was beneficial in an individual case. Recently Gold and his associates^{7,8} came to the same conclusions concerning the xanthine derivatives and digitalis. Others^{4,19} have found that digitalis actually induced anginal attacks. In a study of trichlorethylene by Willius²³ the results were unsatisfactory in the majority of patients. The findings of Riseman and Brown¹⁹ are somewhat difficult to interpret. Their patients were relieved of angina to the same degree by all the drugs used, including a placebo; however, using a modification of the two-step exercise tolerance test of Master,^{15b} they found that certain xanthine derivatives and quinidine alone gave objective evidence of improvement in half the patients; other drugs produced little or no improvement. They observed striking differences among the xanthine derivatives.¹ This work requires confirmation.

Material and Methods. This study was carried out on 116 ambulatory patients attending our angina pectoris clinic. The series was composed of 90 men and 26 women whose ages varied between 35 and 75 years. These patients were for the most part in very poor circumstances; many were receiving relief benefits, and almost all were out of work. In order to gain a comprehensive view we have therefore considered it of value to include in this report the results obtained by one of us (A. M. M.) in patients seen in office practise. In this group there were 60 males and 25 females. About 75% of the entire series were Jewish, the remainder including many nationalities. The period of observation ranged from 6 months to 4 years. Each patient was seen weekly or biweekly.

All the patients studied presented an anginal syndrome, related to effort or excitement, with evidence of coronary artery disease as revealed by abnormalities in one or more of the following: physical examination, blood pressure, Roentgen ray, fluoroscopy, electrocardiogram, exercise tolerance test and vital capacity. In approximately one-third of patients there was a history of one or more attacks of coronary occlusion.

The following routine of medication was employed in the clinic. When first seen, the patient was given a placebo, 1 grain of milk sugar 3 or 4 times daily, unless he was very ill. This was continued 2 to 4 weeks, until its effect on the precordial pain was determined. The patient was then given another drug for a similar trial period. In this way, the drugs listed

in Table 1 were administered successively, the average number of drugs received by each patient being 7. When a drug was associated with improvement it was usually replaced by a placebo, and then repeated one or more times. Thus the effect of each drug, as compared to that of the placebo, was studied several times in the same patient. When a new drug was given the patient was usually aware of the fact, for very little attempt was made to disguise the different preparations. However, the drugs in tablet form, such as milk sugar, phenobarbital, codeine, aminophyllin, had a similar size and shape. As a rule, the maximum clinical dose of each drug was given during some period of its trial. Thus theobromine was given in 7.5 to 10-grain doses, and aminophyllin in 3-grain doses, 4 to 6 times daily; digitalis was pushed to full therapeutic dose, and then a maintenance dose continued.

The effect of a drug was judged by the statement of the patient concerning the frequency and severity of precordial pain. Usually this was best evidenced by the distance the patient could walk without experiencing pain and the number of spontaneous attacks. A specially arranged chart, minutely analyzing the pain, was filled out at each visit in order to insure uniformity of judgment as to the effect of the drug and the condition of the patient was recorded as "better," "same" or "worse."

The following case report illustrates the manner of medication followed and the usual therapeutic response.

Case Report. B. K., No. 36-10885, an unemployed Jewish accountant, aged 60, came to the clinic November 18, 1936, for increasing substernal pain on effort during the preceding 2 years. He frequently experienced 5 to 10 attacks daily. He had had hypertension for 10 years. Physical examination showed his blood pressure to be 210/100 mm. Hg. The lungs were clear. The heart was not enlarged, but the aorta was elongated on fluoroscopic examination. The second aortic sound was accentuated. The vital capacity was 2000 cc.* The exercise tolerance test was normal. Electrocardiogram showed left ventricular preponderance, a diphasic T-1 and an absent initial positive deflection in the chest lead, indicating previous myocardial infarction.

He was given milk sugar, 1 grain 3 times a day, and felt better for 1 week; but not the next. He then received aminophyllin and phenobarbital each for 2 weeks, but the number of attacks increased. He then received milk sugar for several weeks and was improved. During the next month he was given phenobarbital and suffered only 2 or 3 attacks a week. During the next 2 weeks digitalis was given without any effect at first, but during the second week the number of attacks increased. Phenobarbital was again given but there was no improvement. Aminophyllin, and later nitroglycerin, was without effect. Phenobarbital was resumed and after several weeks the patient became free of pain. He was then given no medication and continued to feel well for 2 months. The pain returned at this point, but disappeared after bromides were taken. It reappeared after a month and was not improved by phenobarbital. Nitroglycerin was then administered and the patient had little or no pain. During the past winter and spring he has felt well while taking bromides, theobromine, and for 4 months, milk sugar alone.

Results. Our findings are recorded in Tables 1 and 2. In Table 1 is noted the number of patients receiving a drug and the effect on each patient to whom it was given for at least 1 month. If the drug consistently reduced the frequency and severity of attacks of pain, it was considered a complete success; if it reduced these at least half the time it was used, it was labeled a partial success. The sum of these is the number of patients improved. In Table 2 is

noted the effect of the drug each time it was used, that is, whether the pain was made better or worse during each 2 to 4 week period in which it was used. Clinic and private patients are separated.

It will be seen (Table 1) that there were few complete successes, that is, few patients were consistently helped by a particular drug. Even when the partial successes are included, the percentage of patients improved was still low, almost always under 25%, the highest being 31%. When the number of times, that is, the number of 2 to 4 week periods, each drug was used is considered (Table 2), the pain was made better more frequently, the highest percentage being 50. The results are similar in clinic and private patients. It will be noticed that the percentage range for the majority of drugs was limited; thus 15 to 25% of patients were relieved no matter what drug was used, and most drugs were successful 40 to 50% of the time they were given. When the use of a drug was not associated with relief, there was no effect or not infrequently the pain was increased; here, too, the percentage range was within narrow limits. Such uniform results suggest that it was not a particular drug, but merely the factor of receiving a medication, that gave relief, and that exacerbation of pain was also coincidental. This belief is definitely confirmed by the results obtained with a placebo, 1 grain of milk sugar. It was a complete success in 13 patients, and improved 30% of all the patients receiving it. In addition, it was associated with diminution of pain 52% of the times it was used. These results were almost identical with the best obtained with any other drug, namely aminophyllin, with which the percentages were 31 and 50 respectively. Obviously one cannot ascribe a specific effect to a drug when its action is no better than that of an inert substance. The improvement noted must depend on psychologic factors, a point we shall shortly discuss. In this way may best be explained a small group of patients who were helped by every drug they received and another group who were not relieved by any drug for long periods. Such a course is quite different from that encountered in the majority of patients for even patients with a very advanced degree of coronary artery disease experienced periods of freedom from pain either spontaneous or while receiving some medication. There was little difference in response of the patients to the individual drugs, except perhaps in the case of sodium nitrite, which, unlike nitroglycerin, seemed to exert an adverse effect on pain. Frequently, dispensing a new drug gave relief for a time, but this usually wore off, until another drug was substituted. Although the percentage of success with digitalis was not high, it was not found to aggravate the anginal syndrome in any case, as had been suggested.^{4,19} Nor did the study bear out an impression previously entertained by us of the value of alcohol. Like the other drugs, usually it was of benefit only temporarily. This was true also of codeine and dilaudid, in spite of adequate

TABLE 1.—RESULTS OF DRUG THERAPY.

Drug.	No. of patients.	Complete success.	Partial success.	Total success (per cent).
1. ALCOHOL:				
Clinic	21	2	7	43
Private	54	6	4	18
Total	75	8	11	25
2. AMINOPHYLLIN:				
Clinic	58	6	15	36
Private	69	14	4	26
Total	127	20	19	31
3. ASPIRIN:				
Clinic	24	1	5	25
Private	9	0	0	0
Total	33	1	5	18
4. BROMIDES:				
Clinic	21	0	5	24
Private	12	0	4	33
Total	33	0	9	27
5. CHLORAL HYDRATE:				
Clinic	7	0	1	14
Private	28	2	2	14
Total	35	2	3	14
6. CHLORAL AND BROMIDES:				
Clinic	21	3	5	38
Private	19	0	1	5
Total	40	3	6	22
7. CODEINE:				
Clinic	24	3	6	37
Private	29	1	2	10
Total	53	4	8	23
8. DIGITALIS:				
Clinic	23	0	3	11
Private	Not used			
Total	23	0	2	11
9. DILAUDID:				
Clinic	33	2	7	27
Private	54	8	1	17
Total	87	10	8	21
10. LUMINAL:				
Clinic	70	5	13	26
Private	36	2	2	11
Total	106	7	15	21
11. MYORGAL:				
Clinic	26	3	1	15
Private	4	2	0	50
Total	30	5	1	20
12. NITROGLYCERIN:				
Clinic	36	1	3	11
Private	53	4	7	21
Total	89	5	10	17
13. PHYLLICIN:				
Clinic	8	0	1	12
Private	13	1	1	15
Total	21	1	2	14
14. MILK SUGAR:				
Clinic	83	13	12	30
Private	Not used			
Total	83	13	12	30
15. SODIUM NITRITE:				
Clinic	11	0	1	9
Private	Not used			
Total	11	0	1	9
16. THEOBROMINE:				
Clinic	52	4	4	15
Private	7	0	0	0
Total	59	4	4	14

TABLE 2.—CONDITION OF PATIENTS AFTER THERAPY.

Drug.	Times used.	Per cent better.	Per cent worse.
1. ALCOHOL:			
Clinic	106	44	18
Private	141	54	13
Total	247	50	15
2. AMINOPHYLLIN:			
Clinic	153	45	25
Private	279	53	16
Total	432	50	19
3. ASPIRIN:			
Clinic	54	30	35
Private	9	55	22
Total	63	33	33
4. BROMIDES:			
Clinic	42	24	7
Private	13	53	31
Total	55	31	13
5. CHLORAL HYDRATE:			
Clinic	14	21	29
Private	71	52	20
Total	85	47	21
6. CHLORAL AND BROMIDES:			
Clinic	68	50	21
Private	44	36	15
Total	112	45	19
7. CODEINE:			
Clinic	50	40	16
Private	54	41	24
Total	104	40	20
8. DIGITALIS:			
Clinic	88	36	22
Private	Not used	—	—
Total	88	36	22
9. DILAUDID:			
Clinic	105	33	27
Private	169	57	16
Total	274	48	20
10. LUMINAL:			
Clinic	241	41	24
Private	70	44	6
Total	311	42	20
11. MYORGAL:			
Clinic	53	43	1
Private	4	50	0
Total	57	44	12
12. NITROGLYCERIN:			
Clinic	91	40	30
Private	159	54	14
Total	250	49	2
13. PHYLLICIN:			
Clinic	12	33	42
Private	24	45	21
Total	36	42	28
14. MILK SUGAR:			
Clinic	249	52	14
Private	Not used	—	—
Total	249	52	14
15. SODIUM NITRITE:			
Clinic	22	23	41
Private	Not used	—	—
Total	22	23	41
16. THEOBROMINE:			
Clinic	106	42	26
Private	9	33	67
Total	115	42	21

i. e., number of 2 to 4 week period.

doses. Several other drugs, including potassium iodide, trichloroethylene, pancreatic hormone, and so on, while used in too few patients for statistical analysis, acted like the drugs listed. Nitroglycerin was found to relieve attacks, but not to prevent them in a significant number of patients.

Discussion. Since improvement in angina pectoris was no greater with a large number of drugs than with a placebo, it is clear that success in the treatment of this syndrome does not depend upon the use of any one drug or group of drugs. There is no convincing evidence that drugs such as aminophyllin, theobromine and its compounds, tissue extracts, and so on, which are supposed to dilate the coronary arteries, actually do so when given orally in ordinary clinical doses. In fact, the experimental results are inconclusive.^{5,9,22} When a drug is associated with relief of pain the effect may be entirely coincidental, for patients not infrequently have spontaneous remissions of anginal attacks for varying periods, in the absence of medication. A patient will often volunteer the information that for no obvious reason at all he has felt much better during the preceding week or two, and such an improved state may continue. Furthermore, the occurrence of anginal pain is intimately related to numerous events in the daily life of the patient: the amount of exertion, the diet, the presence of constipation, the weather; a change in any of these may influence the number and severity of attacks, an effect which may seem to be due to whatever drug is being taken at the time. Of paramount importance, however, we have found the nervous makeup and emotional status of the patient. A diminution in domestic or financial difficulties, some encouraging event, these have lightened a hitherto persistent anginal syndrome. The following cases illustrate this point:

CASE 2. A. G., a man of 64, has had substernal pain and a sense of choking on walking for 10 years. His electrocardiogram shows a small, slurred polyphasic *QRS* measuring 0.11 sec. Following 1929, his symptoms varied directly with the condition of the stock market, the coincidence becoming obvious even to himself.

CASE 3. Another male patient, H. L., aged 53, has had precordial pressure related to effort for some years. The blood pressure is 160/104 mm. Hg. The electrocardiogram shows a *P-R* interval of 0.24 sec., and the exercise tolerance is reduced. This patient was dean of one of the schools at a university and, although possessing a genial nature, was unable to get along with the president of the university, a most overbearing person. One and a half years ago an opportunity presented itself for the patient to become head of another college. Because of the increased work and responsibility entailed, we advised against accepting the position. However, he believed that changing his environment would be beneficial and he made this change. Since then, for the past 2 years, he has felt very well and has had little or no pain, in spite of the fact that he is working much harder than before.

A new medication, a new physician, a new type of therapy may bring relief. Thus, the average patient feels improved during the first few weeks of attendance at the clinic no matter what drug he

receives. This probably explains the reports of good results with numerous drugs. While anginal pain results from myocardial ischemia, it is apparent that a factor other than coronary artery disease is essential, and that is the emotional or nervous one. In fact, it is our impression that typical anginal pain may occur in the absence of any pathologic changes in the coronary arteries, a subject which will be discussed in a future report. Even in cases with coronary disease, the severity of the anginal syndrome is determined largely by the nervous or emotional state of the patient. One of our sickest patients, a man who had suffered at least three coronary occlusions, and who for years complained of intractable precordial pain, lost this symptom almost entirely when his invention proved a great financial success. Yet he died suddenly during this period of well being. It is for this reason that the response to any therapeutic measure must be carefully weighed. There are a number of patients who are helped for a time by practically any drug; there are others, however, who respond not at all to any drug or other type of therapy. In practise, as one would expect, sedatives have proven slightly more effective than other drugs, because of their quieting influence. We believe that more careful attention to the psychologic problems of the patient will be rewarded by a greater degree of success than is usually obtained. It is the physician who spends half an hour talking to a patient gaining his interest and confidence who is most apt to help the patient.

Summary. A study has been made of the effect of 16 drugs, including a placebo, milk sugar, on angina pectoris due to coronary artery disease. The drugs included several xanthine derivatives, alcohol, sedatives such as phenobarbital, chloral and bromides, the nitrites, a tissue extract, digitalis and two narcotics, codeine and dilaudid.

No drug was found to exert any specific effect on the anginal syndrome, for the best results were obtained with a placebo, and the number of patients improved ranged between 15 and 30% for all drugs.

No drug was consistently successful in a significant number of cases. Some patients were helped by all drugs, others by none.

The beneficial effects attributed to many drugs in the past may be explained on the basis of insufficient consideration of the significance of the natural course of the anginal syndrome, and particularly, of psychologic factors, in determining the degree of pain. The mildness or severity of the anginal syndrome is often directly dependent on the emotional status of the patient at the time, regardless of the degree of coronary artery disease.

It is concluded that drugs should play a minor rôle in the treatment of angina pectoris. Instead the importance of such measures as rest, dietary restriction, and minute attention to the mental and emotional status of the patient, is emphasized.

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A NECROPSY SURVEY OF CARDIOVASCULAR SYPHILIS WITH PARTICULAR REFERENCE TO ITS DECREASING INCIDENCE.

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COMPREHENSIVE statistical studies regarding the subject of cardiovascular syphilis have appeared infrequently in the literature during the past decade. This is surprising in view of the specificity of antisyphilitic therapy and considering the increasing publicity in both lay and medical publications concerning the advantages of early treatment. Occasional autopsy surveys, particularly large series of cases from one institution, are desirable in order that trends in the incidence of the disease may be observed and it may be determined whether or not modern methods of treatment are of value in preventing the late crippling manifestations of syphilis. This seems especially indicated in view of the well-known opinion of German syphilographers that cardiovascular syphilis has shown a marked increase in frequency since the introduction of arsphenamine. American clinicians are practically uniformly of the belief that early, adequate treatment prevents fatal cardiovascular syphilis, but this view is based almost entirely on clinical experience; it is a fact that cardiovascular syphilis often defies antemortem diagnosis, and consequently statistics based on such data are sub-

ject to error. It is true, of course, that criteria of pathologists vary, and that even at autopsy mistakes in the diagnosis occur; this method is, however, considerably more accurate than clinical investigation.

In the present study, the clinical and pathologic records of 15,000 consecutive cases coming to autopsy between August 5, 1927, and June 15, 1937, were analyzed; those presenting post-mortem evidence of cardiovascular syphilis were studied in detail. The present communication deals only with statistical data relative to the incidence of cardiovascular syphilis in its various manifestations; subsequent publications will consider other features of the study. I believe that autopsy material of the Philadelphia General Hospital is extremely valuable for a study of this type. The institution is a large, general charity hospital. The patients are from that stratum of the population most likely to be syphilitic. A high autopsy percentage is maintained with no selection as to type of case. It is felt that the material represents a fair cross-section of the so-called lower and lower middle classes of society.

Cardiovascular syphilis of all types was encountered in 1040 (6.93%) of the 15,000 cases coming to autopsy. Roughly, 1 patient in each 15 presented evidence sufficient for this diagnosis. There were 192 syphilitic aneurysms (not including aneurysms of the peripheral arteries and central nervous system), 29 of which presented a complicating aortic regurgitation of luetic origin. This latter lesion without aneurysm was found in 216 cases. The remaining 632 cases were examples of simple syphilitic aortitis or the less common cardiovascular manifestations of this infection. Because of the highly controversial nature of the subject, cases with the pathologic diagnosis of syphilitic myocarditis have not been considered in this study, unless there was a definite associated syphilitic aortitis or aortic regurgitation of luetic type. I strongly feel that such an entity exists, but believe that, in my series at least, it is a relatively uncommon finding at autopsy.

In Chart 1 the relative incidence of cardiovascular syphilis in the Philadelphia General Hospital is compared with that of other large autopsy series in northern United States. Ophüls,¹⁴ in 1926, reported the presence of this cardiovascular lesion in 5.43% of 3000 autopsies in the Stanford University series. The Presbyterian Hospital (New York) statistics reported by Lamb and Turner⁷ show 5.1% in 2081 autopsies. This lower incidence during the years that cardiovascular syphilis was probably more prevalent than at present is explained by the fact that this hospital is in part a private institution with a consequent higher type of patient, and also by the fact that their white to negro ratio was 9 to 1, whereas mine was approximately 3 to 2. Reid,^{15a} in 1920, noted a 3.5% incidence in Boston. It is well known that cardiovascular syphilis is less common in Boston than in Philadelphia, due chiefly

to the lower negro population. Reid^{15b} later reported that 7% of the autopsied patients at the Boston City Hospital in 1921 presented evidence of cardiovascular syphilis. Martland's¹⁰ Newark statistics in which 3% of subjects were found to have cardiovascular syphilis are not really comparable, because his figures are based upon coroner's cases, in which an autopsy was done because of sudden death. As will be pointed out, cardiovascular syphilis may be an entirely coincidental finding in patients dying of any acute or chronic disease. It has been my experience that the vast majority of these cases do not die suddenly without previous illness or disability. The low figure of 2.6% reported by Clawson and Bell,¹ in 1927, is probably partly accounted for by a low negro population. Their observation of cardiovascular syphilis as a purely coincidental finding in only 13.5% of cases deserves comment; in roughly two-thirds of my series the syphilitic cardiovascular lesion could not be held responsible for the patient's death, and was merely an additional finding at autopsy.

Philadelphia General Hospital—1927 to 1937—15,000 autopsies.

1040 cases; 6.93%.

Stanford University Series (Ophüls)—1900 to 1923—3000 autopsies.

163 cases; 5.43%.

Presbyterian Hospital (N. Y.) (Lamb and Turner)—1916 to 1930—2081 autopsies.

106 cases; 5.1%.

Boston (Reid)—1909 to 1919—1678 autopsies.

54 cases; 3.5%.

Newark (Martland)—1925 to 1930—3325 autopsies.

101 cases; 3%.

Minneapolis (Clawson and Bell)—1910 to 1926—4577 autopsies.

119 cases; 2.6%.

CHART 1.—Relative incidence of cardiovascular syphilis in various autopsy series in northern United States.

As shown in Table 1, males accounted for 74% of the cases of cardiovascular syphilis of all types, 76% of aneurysms and 81% of syphilitic aortic regurgitation. These figures are in complete agreement with the accepted thought that cardiovascular syphilis is predominantly an affection of the male sex.

TABLE 1.—SEX INCIDENCE OF CARDIOVASCULAR SYPHILIS.

Lesion.	Male.	Female.	Total.
All cases	769	271	1040
Aneurysm	146	46	192
Aortic regurgitation	174	42	216

In regard to race, negroes were responsible for the bulk of each group. As is shown in Table 2, of the entire series, 711 cases

(68%) were found in negroes, though they formed only two-fifths of those studied; there were 326 instances of cardiovascular syphilis in the white race and 3 cases in orientals; 144 of 192 aneurysms (75%) were in the black and 152 of 216 cases of syphilitic aortic regurgitation (70%) were accounted for by the colored race. It is apparent that the greatest proportion of cardiovascular syphilis is found in the negro and that this percentage is only slightly higher in the fatal types of the disease.

TABLE 2.—RACIAL INCIDENCE OF CARDIOVASCULAR SYPHILIS.

Lesion.	White.	Black.	Yellow.	Total.
All cases	326	711	3	1040
Aneurysm	48	144	0	192
Aortic regurgitation	64	152	0	216

In Table 3—age distribution of all cases including aortic regurgitation and aneurysm—79% of all patients were in the age group from 35 to 65; 76% of cases of aortic regurgitation and 80% of aneurysms were found in this particular age distribution. The percentage is remarkably constant for all forms of the disease.

TABLE 3.—AGE INCIDENCE OF CARDIOVASCULAR SYPHILIS.

Age.	Aortic regurgitation.	Aneurysm.	All cases.
Under 21	2	0	3
21 to 30	19	14	52
31 to 40	41	35	156
41 to 50	58	59	308
51 to 60	57	49	274
61 to 70	33	27	189
Over 70	5	8	54
Unknown	1	0	4
Total	216	192	1040

An investigation of the cases from the combined standpoint of race and age revealed the interesting fact that while crippling cardiovascular syphilis (aneurysm or aortic regurgitation) occurred in 50 instances in persons under 35 in this series, in only 4 cases (8%) was one of these affections encountered in a white subject. Aortic regurgitation was the lesion found in all 4 patients, age 15, 26, 30 and 34 respectively. Aneurysms were present on 18 occasions in those under 35, but not once in this age group, and only once below 40 (a 38-year-old male in whom it was a coincidental finding) was a syphilitic aneurysm demonstrated at postmortem in a caucasian. One is forced to conclude that fatal cardiovascular syphilis before the fifth decade is an extreme rarity in whites. It is also considered notable that 20 of the 39 cases of serious cardiovascular syphilis encountered above 65 were in white subjects, whereas the colored race accounts for over 70% of aneurysms and aortic regurgitation in the entire series. Comparing the two races, cardiovascular syphilis is much more prevalent in the negro, attacks that race earlier in life and shows a tendency to develop a more

serious cardiovascular lesion. It must be pointed out, however, that when aortic regurgitation develops, the prognosis is uniformly bad and race has little to do with life expectancy. In this series the duration of life following onset of congestive failure with this lesion was almost exactly the same for the two races, being about $9\frac{1}{2}$ months in each instance.

Trends in the incidence of cardiovascular syphilis have been noted by only a few observers, and several of these reports have been contradictory. However, the majority of communications from the United States have shown some decrease in the frequency, both clinically and at autopsy. White¹⁹ states that he and Jones found 5% of 880 cardiacs as primarily or secondarily syphilitic at the Massachusetts General Hospital in 1928, whereas Cabot at the same clinic in 1914 reported that 12% of 600 cardiac cases were due to syphilis. Thus, in well-studied material there had been a decrease of almost 60% in a 14-year period. Lamb and Turner,⁷ after analyzing 2081 autopsies at the Presbyterian Hospital in New York, stated that 6.4% of autopsied cases in the years 1916 to 1920 showed the presence of cardiovascular syphilis, and that this figure had dropped to 5.5% in the period 1921 to 1925, and to 4.1% in the years 1926 to 1930. Coombs³ believes that the death rate in England from aneurysm is decreasing, but gives no statistics. Three clinicians,^{6,16,17} who have been on the wards at the Philadelphia General Hospital during the past 25 years, have informed me that a decrease in the incidence of cardiovascular syphilis has been very apparent during that period.

Against these opinions is the report of Cormia⁴ from Montreal, based upon 7416 autopsies from 1910 to 1934; this author concluded that the incidence of cardiovascular syphilis as a fatal disease is decreasing but slightly. Swinging far in the other direction is the report of Langer,⁸ in Germany, who, after an analysis of 23,105 autopsies from 1917 to 1925, concluded that the incidence of syphilitic aortitis has shown a marked increase since the introduction of organic arsenicals in treatment. His curves show a sharp increase in the incidence of cardiovascular syphilis beginning in 1912 and continuing thereafter; he states in addition that, whereas 33% of syphilitics had aortitis prior to the use of arsphenamine, 83% had developed this lesion during the years when this drug was employed. Heller,⁵ also in Germany, makes the statement that the number of aneurysms has quadrupled since the introduction of arsphenamine. It is impossible in any way to explain the findings of these last two investigators; one can only say that they have not been duplicated by careful clinical and pathologic studies in any other country or institution in the world.*

* Not forgetting the *post-propter* fallacy, it must not be assumed that, because the incidence was increased after the introduction of arsphenamine, it was necessarily due to the arsenic. The many changes in Germany since 1917 suggest at least other possible causes.—EDITOR.

Concerning the incidence of syphilis in general, reports are also somewhat conflicting. Nelson,¹³ in 1936, stated that syphilis in the state of Massachusetts had shown a definite decrease, there being a reduction of 70% in syphilis in pregnant women over a 15-year period; there had also been a 30% decrease in early syphilis and a 32% decrease in neurosyphilis over a 5-year period. Moore,¹¹ however, in the same year stated that syphilis in Baltimore was actually more prevalent, there having been a progressive increase in the reported cases between the years 1929 and 1933. One wonders whether the latter author was not really showing an increase in the efficiency of reporting the cases, rather than an actual increase in the number of cases of syphilis.

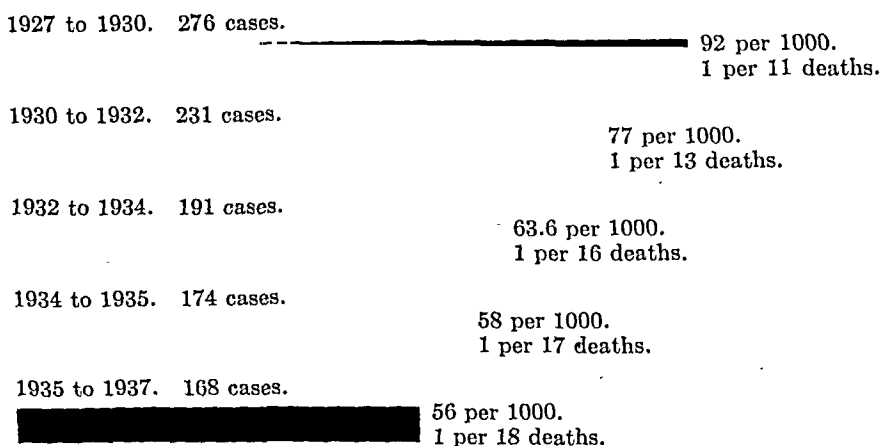


CHART 2.—Decreasing incidence of cardiovascular syphilis at Philadelphia General Hospital.

For purposes of contrasting the relative incidence in my own material, the 15,000 autopsies were divided into consecutive groups of 3000 cases each. Each group represents a period of 18 to 30 months, the variation depending upon the increasing and changing number of autopsies from year to year. Chart 2 summarizes the results of this comparison for all types of cases. The first group coming in the years 1927 to 1930 showed a total incidence of 9.2%; this subsequently dropped to 7.7% in 1930 to 1932, to 6.36% in 1932 to 1934, to 5.8% in 1934 to 1935, and finally to 5.6% in 1935 to 1937. Or, roughly, cardiovascular syphilis, which was encountered in 1 case in every 11 at autopsy at the beginning of the decade, was found in only 1 case in 18 at the end of the 10-year period.

Chart 3 graphically shows a similar decrease in the incidence of syphilitic aneurysms (excluding aneurysms of the peripheral arteries and central nervous system). There were found 17 per 1000 cases in 1927 to 1930, 14 per 1000 cases in 1930 to 1932, 12.3 per 1000 cases in 1932 to 1934, 11.3 per 1000 cases in 1934 to 1935, and finally 9.3 per 1000 cases in 1935 to 1937. Or, briefly, a decrease

from 1 aneurysm per 59 deaths to 1 per 108 deaths over a 10-year period. The statistics of Lucké and Rea,⁹ which were collected from the Philadelphia General Hospital and the Hospital of the University of Pennsylvania covering 12,000 autopsies from 1867 to 1916, are included for further contrast. These authors apparently included arteriosclerotic aneurysms in their study. However, since syphilis accounts for 85% of aneurysms of the aorta and great vessels, and since the 6% negro admission rate, cited by Lucké and Rea, had risen to almost 40% by the time of my survey, I believe there is justification for comparison of these figures. As a matter of fact, if one corrects for both the inclusion of arteriosclerotic aneurysms and for the increase in the negro population, the net would be considerably higher than 23 cases per 1000. I believe that one may conclude from this study that syphilitic aneurysms are less than one-half as frequent at present as before the introduction of salvarsan in therapy.

1867 to 1916. Lucké and Rea. 278 cases in 12,000 autopsies.

23 per 1000.
1 per 43 deaths.

1927 to 1930. 51 cases.

17 per 1000.
1 per 59 deaths.

1930 to 1932. 42 cases.

14 per 1000.
1 per 71 deaths.

1932 to 1934. 37 cases.

12.3 per 1000.
1 per 81 deaths.

1934 to 1935. 34 cases.

11.3 per 1000.
1 per 88 deaths.

1935 to 1937. 28 cases.

9.3 per 1000.
1 per 108 deaths.

CHART 3.—Decreasing incidence of syphilitic aneurysms at the Philadelphia General Hospital.

As is shown in Chart 4, there has also been a progressive decrease in the incidence of syphilitic aortic regurgitation over the 10-year period. The combined incidence of aortic regurgitation alone, plus aortic regurgitation complicated by aneurysm, was 21 per 1000 in the first 3000 cases, 17 per 1000 in the second group, 16.6 per 1000 in the third series, 14.6 per 1000 in the fourth group, and 12.6 per 1000 in the final 3000 autopsies.

Thus far these figures have dealt only with cardiovascular syphilis as an isolated autopsy finding and not as a cause of death. As stated, this lesion was observed at postmortem in 1040 of 15,000 autopsies (6.93%). However, in only 339 instances (2.26%) was

the syphilitic cardiovascular lesion the direct, or an important contributing factor in the death of the patient. Thus in roughly two-thirds of the cases it was a coincidental finding; and, while it might have ultimately caused death, it actually had little to do with the exitus. It should be constantly kept in mind that the mere anatomic demonstration of cardiovascular syphilis at the autopsy table does not mean that this lesion was the cause of death or even of the symptoms observed. Unless aortic regurgitation, aneurysm, coronary orificial stenosis, or myocarditis, alone or together, are present, there is no reason for circulatory insufficiency 1927 to 1930. 63 cases.

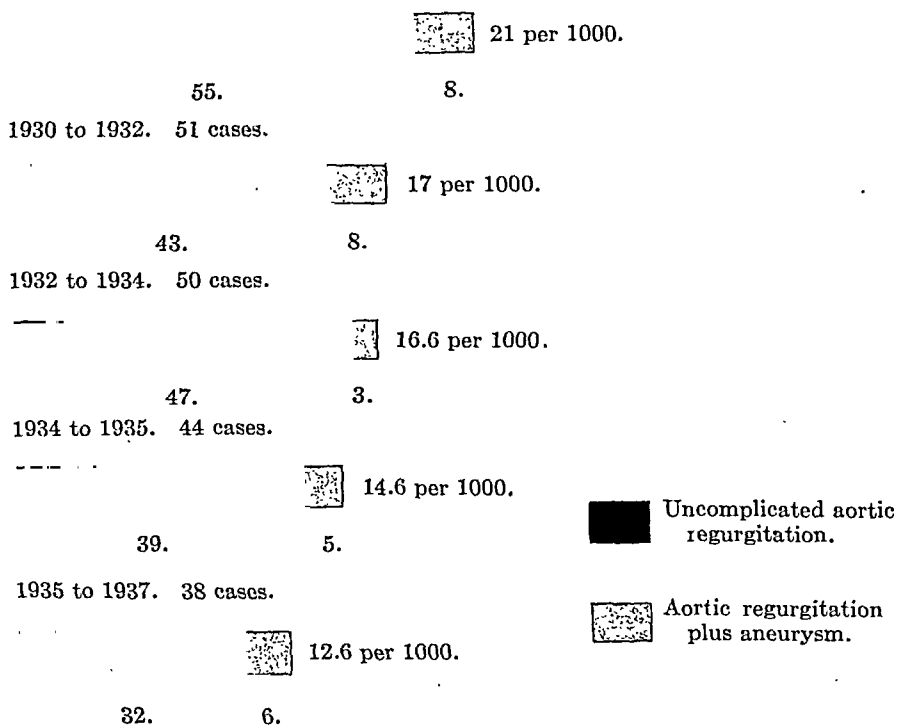
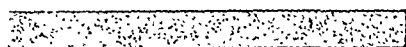


CHART 4.—Decreasing incidence of syphilitic aortic regurgitation at the Philadelphia General Hospital.

to ensue. My clinical and pathologic experience has led me to the conclusion that many cases of heart failure labelled as syphilitic because of positive serology, an aortic systolic murmur and an accentuated basal second sound, turn out at postmortem to be hypertensive or arteriosclerotic with syphilis present as an entirely coincidental finding, or even entirely absent as far as the circulatory system is concerned. I have recently seen a case which clinically presented evidence of congestive heart failure, a basal diastolic murmur, peripheral signs of aortic regurgitation and a 4+ Wassermann reaction. Because the patient was an alcoholic and also had a peripheral neuritis, crystalline vitamin B₁ was administered,

digitalis and antisyphilitic therapy being withheld. Within a period of 10 days compensation had been restored and the diastolic murmur had disappeared. Here there was every positive sign for a clinical diagnosis of syphilitic cardiovascular disease, yet the presence of syphilis actually had nothing to do with the cardiac disability.

1927 to 1930. 96 cases.

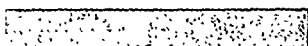


32 per 1000.

40 cases.

56 cases.

1930 to 1932. 73 cases.

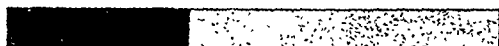


24.3 per 1000.

30 cases.

43 cases.

1932 to 1934. 70 cases.



23.3 per 1000.

26 cases.

44 cases.

1934 to 1935. 54 cases.

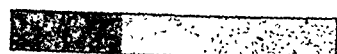


18 per 1000.

26 cases.

28 cases.

1935 to 1937. 46 cases.



15.3 per 1000.

16 cases.

30 cases.



Aneurysms.



All others.

CHART 5.—Decreasing incidence of syphilitic cardiovascular disease as a cause of death at the Philadelphia General Hospital.

In Chart 5 the decreasing incidence of cardiovascular syphilis as a direct, or a directly contributing factor in the death of the patient is shown. In the first 3000 cases the lesion was the cause of 3.2% of all deaths; it then steadily decreased, to 2.43% in the years 1930 to 1932, 2.33% in 1932 to 1934, 1.8% in 1934 to 1935, and finally to 1.53% in 1935 to 1937. Thus syphilitic cardiovascular disease as a cause of death has shown a decrease of well over 50% in this material in a 10-year period.

To emphasize how striking is the decreasing death rate from cardiovascular syphilis, Chart 6 compares graphically the changing incidences of cardiovascular syphilis and tuberculosis as causes of death. The figures for tuberculosis are deaths per 100,000 general population in Philadelphia, whereas those for cardiovascular syphilis are deaths per 3000 autopsied hospital population in the Philadelphia General Hospital. It is worthy of note that the decrease

is actually sharper and more marked in cardiovascular syphilis than in tuberculosis, which is generally conceded to be a rapidly decreasing disease.

The definite decrease in both the incidence of cardiovascular syphilis and its lessening importance as a cause of death must be explained. The difference is too marked to be attributed to the variation in material from year to year. The possible objections to the study are two: First, it might be said that the type of patient at the Philadelphia General Hospital is changing. During the past 10 years the percentage of negroes in the postmortem material has remained practically stationary, being 38.5% at the beginning of the study and 39.3% in 1937. Thus the racial factor has not

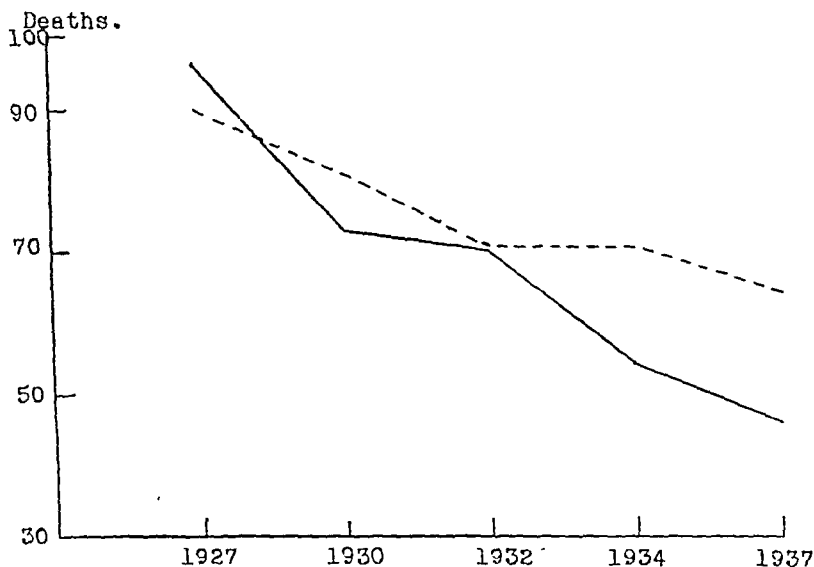


Fig. 6.—Comparison of decreasing death rates of tuberculosis and cardiovascular syphilis.

— Cardiovascular syphilis—deaths per 3000 autopsied population at Philadelphia General Hospital.
 - - - Tuberculosis (all forms)—deaths per 100,000 general population, City of Philadelphia.

changed. Neither has there been any variation in the ratio of sexes coming to autopsy. The other possible variation in the hospital population occurred early in 1936 at which time, due to a change in the policy of the hospital administration, the number of senile patients admitted to the psychopathic wards was considerably decreased. This fact would tend to lower the average age incidence of patients coming to autopsy and, since cardiovascular syphilis is primarily a disease of the middle decades of life, it should increase rather than decrease the incidence, other factors being unchanged. This change in admission policy may possibly explain the fact that the decrease in the last group of 3000 cases (Chart 2) was not as great as one would anticipate from previous trends.

The second possible objection is that perhaps the criteria of the pathologists performing the autopsies are changing, and that, whereas at the beginning of the series perhaps they were content to label minor intimal wrinkling syphilitic, they are now demanding absolute gross evidence or microscopic confirmation. That this might be a factor I am willing to concede, particularly as slight luetic aortitis is often very difficult to identify at autopsy, especially with coëxisting atherosclerosis. That it is not the real explanation, however, is shown by the fact that the incidence of syphilitic aneurysms has also decreased, and also that the instances of severe or fatal cardiovascular syphilis have decreased more markedly than the disease in general. In other words, not only has there been a decreased incidence of cardiovascular syphilis, but the severity of the lesion, once it has developed, has also lessened.

The accurate explanation of the decreasing incidence is probably based on more efficient treatment; there are two reasons why it is apparent in the decade 1927 to 1937. First, it is well known that more and more routine serum tests are being done and that each year a larger group of patients, especially early luetics and latent seropositive cases, are receiving antisymphilitic therapy. This fact alone is of tremendous importance. Second, and probably of even greater significance, is the long, latent period between the chancre and the appearance of clinical cardiovascular syphilis and death. This has been shown by many authors to average between 15 and 20 years. Salvarsan was not introduced in the treatment of syphilis until about 1912, and it was several years later before mass treatment was begun. Thus, treatment of early syphilis started, for example, during the World War, could not be expected to materially influence statistics until the late 1920's and early 1930's.

It has been well shown from a clinical standpoint that early, adequate treatment in the majority of cases will protect an individual against clinically recognizable cardiovascular syphilis. Moore, Dangle and Reisinger¹² did not find a single case of cardiovascular syphilis during the period of observation among 117 patients who had received three or more courses of arsphenamine plus *interim* heavy metal, whereas in patients in the same study receiving less than 8 injections of arsphenamine, 9.6% developed cardiovascular syphilis. The Coöperative Clinical Group¹⁸ has compared its 907 cases of early treated syphilis with Bruusgaard's series of 145 untreated, early syphilitics, and show that the late crippling manifestations are much less common in the treated group. The Coöperative Clinical Group has also stated² that patients adequately and regularly treated for early syphilis, and followed 3 to 20 years after infection will be almost exempt from cardiovascular involvement. As a matter of fact, inadequate treatment is considerably better than no treatment at all.¹⁸ I believe that it may be said with caution that even inadequate treatment may, in some cases "immunize" the patient against subsequent cardiovascular involve-

ment. The above authors have proved by careful clinical studies that treatment prevents cardiovascular syphilis; I believe that my statistics show that we are seeing the results in the unselected general population of Philadelphia.

Summary. 1. Syphilitic cardiovascular disease was encountered in 6.93% of 15,000 autopsies at the Philadelphia General Hospital. The incidence of syphilitic aortic regurgitation was 1.44% and of syphilitic aneurysm 1.28%.

2. Statistical data concerning sex, color and age are given.

3. Syphilitic cardiovascular diseases, in all forms and as a cause of death shows a definitely decreasing incidence during the 10-year period, 1927 to 1937.

4. It is believed that the decreasing incidence may be explained by modern methods of therapy.

I am indebted to Dr. R. P. Custer for his advice and friendly criticism in the preparation of this paper.

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ON THE TREATMENT OF RAYNAUD'S DISEASE WITH PAPAVERINE INTRAVENOUSLY.

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Raynaud's disease⁶ or intermittent spasm of the digital arteries with or without nutritional changes occurs most frequently in women. There are attacks of discoloration and numbness of the digits upon

exposure to cold, with recovery on rewarming. Hours may elapse during which the blood flow to the fingers is absent or is just perceptible.^{4a} The present report includes studies upon 5 patients, 4 women and 1 man; 2 of the women had trophic changes of the fingers.

Since the cause of the symptoms is the transient loss of circulation to the digits due to closure of the digital artery^{4b} in response to cold, it is to be expected that vasodilators of the nitrite or isoquinoline types might release the smooth muscle spasm. The waxy pallor present in these patients during an attack is due to spasm of the minute vessels in the skin. In order to release this spasm we had recourse to histamine hydrochloride administered by iontophoresis. Despite the fact that histamine dilates the minute vessels,⁷ it increases the arterial spasm of the arteries,² a condition not desirable in these patients. Such procedures might be expected to relieve the acute attack and also alleviate the trophic changes which are secondary to the diminished blood flow through the arteries in the early stages. The nitrites have been tried and discarded because of the profound effect on blood pressure from adequate doses and also because the effects are evanescent and often followed by severe headaches.

Our study was limited to the intravenous injection of papaverine hydrochloride (a benzyl-isoquinoline derivative) in doses of from 60 to 120 mg. given 3 times a week, usually before and after histamine iontophoresis, for from 8 to 12 weeks. Fifteen to 30 seconds following the administration of the papaverine, there are intense flushing of the face, perspiration of the skin, and marked increase in the depth of breathing. The electrocardiogram is unchanged, except for an increase in the heart rate from an average of about 75 to about 100 beats per minute. The blood pressure rises an average of 12 mm. of mercury in both the systolic and diastolic levels. These effects last less than 5 minutes. Oscillometric measurements of the forearm show no changes throughout a period of 45 minutes following the injection.¹ Application of the histamine ointment to the skin followed by iontophoresis at from 20 to 60 milliamperes for 3 to 9 minutes causes redness of the hand and wheals on the wrist and forearm.

The circulation of the hand was studied by the 5 methods to be described in a forthcoming communication. These are (1) the pressure plethysmograph method of Hewlett⁵ which measures rate of blood inflow; (2) the simple plethysmograph which measures the volume changes in the hand; (3) the thermopyle thermometer for measuring skin temperature; (4) the skin calorimeter for the measurement of available heat; and (5) capillary observations at the nail fold.

(1) The rate of blood inflow in these 5 patients averaged 6.6 cc. per 100 cc. hand volume per minute, as compared with a rate of 8.6 cc. as the average for 48 control subjects. After prolonged treat-

ment with papaverine, the average rate of flow rose to 8.79 cc. or an increase of 33%. When this optimum rate was reached, the injections of papaverine no longer resulted in an increased rate of flow. This method also yields figures of hand capacity, which averaged 7.8 cc. before any treatment, and rose to the normal figure of 11.5 cc. after prolonged treatment, a rise of 47%. Following iontophoresis there was an increase in the rate of blood flow of 13% and a capacity change of 33% over the pre-injection level. After papaverine, iontophoresis usually decreased the inflow rate, but increased further the capacity of the hand.

(2) The simple plethysmograph showed that after the intravenous injection of papaverine there was an increase in the volume of the hand within the plethysmograph of from 5 cc. to 34 cc. with an average of 13.8 cc. When papaverine is injected after iontophoresis, the volume increase of the hand is greater than when no histamine had been applied. This volume increase averaged 16.4 cc. and is in addition to that which presumably follows iontophoresis. These results confirm the figures obtained with the pressure method.

(3) The skin temperature rose after the injection of papaverine from 0.27° C. to 4.8° C. In one patient the right index finger gained 2.7° C., while the right middle finger gained only 1.7° C. because the former was originally the colder. Histamine iontophoresis caused a drop in the temperature of the skin of from 0.1 to 5.7° C. After papaverine, the drop in skin temperature was never greater than 3.4° C. However, when papaverine is injected after iontophoresis, there is always a rise in skin temperature. These results confirm the findings with the other less localized methods.

(4) The calorimeter thermocouple showed, after papaverine, an increase in heat output of the skin of the finger in 3 of the 5 patients. The lack of effect in the other 2 is due to factors which cannot be discussed here due to lack of space.

(5) The capillary tufts at the nail fold were few in number, tortuous, and in the male patient, very dilated, before treatment, and the blood flow through them was sluggish or stopped completely. Fifteen to 30 seconds after the injection of papaverine, the flow of blood in the tufts increased in speed so that soon the blood flowed as a continuous stream which appeared to us to be faster than in control untreated subjects. Histamine iontophoresis caused an increase in the number of capillary tufts visible under the microscope and also slightly increased the speed of blood flow. After papaverine, the iontophoresis of histamine decreased the rate of flow through the tufts.

These large doses of papaverine seemed to depress somewhat the sensorium of the patients, but never to such an extent that they could not carry on immediately following the injection. At no time was there any evidence of desire for the drug other than for the relief it afforded the symptoms. After a week or two of treatment, the

condition of the hand would improve sufficiently so that the need of relief was not so obvious to the patient. With no evidence of addiction from papaverine, it seems unfortunate that the drug should be on the restricted list, making it somewhat difficult to obtain readily.

With the advent of warm weather, it has been possible to discontinue all treatment. Three of the patients have been symptom-free from April to the present time. The other 2 have been under treatment until recently and have been symptom-free since May. How permanent the effects of the treatment will be only the advent of winter will tell. However, it is felt that the intravenous injections of large doses of papaverine have definitely helped all the members of this small series.

Summary. 1. The vascular status of the hands of five patients with Raynaud's disease has been studied.

2. Treatment with histamine iontophoresis to the hands and papaverine hydrochloride intravenously in doses from 60 to 120 mg. three times a week has led to (a) an objective increase in the vascular bed volume and the rate of blood inflow of the hand; (b) a complete alleviation of the syncope, cyanosis, and pain from exposure to cold; (c) the healing of trophic lesions when these were present.

3. No addiction and little cerebral depression occurs from the papaverine, despite long continued treatment (6 to 8 months).

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SYMPATHOMIMETIC STIMULANTS IN ACUTE CIRCULATORY FAILURE OF PHENOL SHOCK.*

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ACUTE circulatory failure is caused by changes in relatively few fundamental mechanisms, since there are only three major variables

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in the circulation, namely: cardiac activity, peripheral resistance and blood volume. During circulatory failure from alterations in one or more of these mechanisms, compensatory changes occur in the other variables. Theoretically, the treatment of circulatory failure should be directed at the original seat of action of the causal factor, rather than the other components of the circulation, which are presumably already operating at a maximum to combat the collapse. These considerations are especially pertinent in selecting appropriate circulatory stimulants from the epinephrine-ephedrine group of sympathomimetic amines. Some of these compounds are potent cardiac stimulants with relatively little effect on peripheral resistance; others are more active vasoconstrictors than cardiac stimulants; still others are also effective as central nervous stimulants. It has been shown recently, in this laboratory, that there are great differences in the relative proportions of cardiac and peripheral actions of these agents, when the responses of vessels of isolated peripheral organs and of isolated hearts are compared with each other and with the total pressor effects in the intact organism.^{3,4} In view of these differences in the mechanisms of circulatory failure, it seems obvious that these amines should not be used indiscriminately and interchangeably, but only with proper appreciation of their special spheres of action.

As part of a general study of the considerations governing the choice of these amines as stimulants under various conditions, we have investigated their effects on isolated peripheral vessels and hearts separately, and attempted to apply the information so obtained to the treatment of circulatory collapse produced experimentally in various ways. This paper presents results on the potency of these amines in raising blood pressure previously lowered to shock level by phenol poisoning. Phenol was selected because it has a certain predilection for depressing cardiac muscle, and the circulatory failure so produced is the result of direct cardiac failure. Therefore, a comparison of the potency of these amines as circulatory stimulants, in the normal animal and after phenol poisoning should serve to indicate their relative value in the treatment of collapse of cardiac origin. In later publications, results in other types of circulatory failure will be considered. Briefly, the results obtained indicate that the amines tested are of unequal merit, under the conditions, and some, actually undesirable or dangerous.

Methods. Cats were used throughout, and generally anesthetized with urethane gastrically, in a dose of 1.5 gm. per kilo, body weight. In a few cats, Dial, pentobarbital, or chloritone was used with substantially the same results as to circulatory reactions. The cats were atropinized with 1 mg. atropine per kilo subcutaneously, so as to permit blood pressure changes without complications from vagus action. Blood pressure was recorded from the carotid artery according to the usual technique, and all injections were made into a cannulated femoral vein. At the beginning of each experiment, 2 or 3 spaced injections of epinephrine were made to demonstrate, by the uniformity of the pressor response, that the cat was

in a substantially stable condition of responsiveness. Then, a series of graduated doses of the amines in question were injected, alternating with epinephrine, until 3 or 4 responses of graded magnitude had been obtained for each agent. The doses were so adjusted that small to moderate pressor responses were obtained, in order that the effect might be more nearly proportionate to the dose used. After an adequate series of control responses, injection of phenol was started, using a 2% solution in physiologic saline solution. The injection of phenol was fixed at a constant rate of inflow which was maintained throughout the remainder of the experiment, and so adjusted that, in about 15 minutes, the blood pressure had fallen to about 50% of the previous level. When this level was reached, injections of the amines were repeated, increasing the doses as necessary, so as to reproduce, if possible, the pressor responses to the same amines before the phenol poisoning. It was found impossible to raise the blood pressure by the same absolute amount as in the control reactions to the majority of the agents used. Therefore, the pressor responses were compared in terms of percentage changes from the blood pressure levels just before the injections. By this rather arbitrary procedure, it was possible to get responses which could be compared with those of the controls. The results were calculated according to the dose of amine required to produce a given degree of change before phenol, as compared with that required for the same percentage change after the phenol. This comparison is expressed as dosage ratios, obtained by dividing the required dose for a given response, after the phenol, by that required for the same effect before the shock state.

A total of 64 cats was used in this study, each cat receiving injections of 3 or 4 amines. The order of injected amines was changed from experiment to experiment so that each amine was used in different relationship to each other and in different animals. The compounds of the phenyl series were injected as few times as possible, in any one animal, since multiple injections of these amines produce tachyphylaxis, which interferes with adequate responses after the first dose. Minimal doses of these latter compounds were used, as another means of avoiding the tachyphylaxis. All the doses in this paper are expressed as the amount per kilo of body weight.*

The results obtained may now be described according to groups of amines which are summarized individually in Table 1.

Catechol Compounds. The chemical composition and structural relationships of different chemical groups in the catechol compounds are indicated by the chemical formulas on p. 799.

Epinephrine. This amine was administered to a total of 32 cats with a median dose of 3.3 gammas (0.001 mg.). Phenol was injected at a median rate of 2.6 mg. per kilo per minute. After the phenol, the dose of epinephrine required was a median of 5.1 gammas for the same percentage increase in blood pressure or a median increase of 1.4 times. Although epinephrine produced an increase of blood pressure to substantially a normal level, the recovery was transitory, the blood pressure returning promptly to the shock level about as rapidly as before the phenol. Therefore, there was no permanent

* We are indebted to Dr. O. Schaumann, of the I. G. Farb. Gesell. Hoechst, through the Winthrop Chemical Company, for the arterenol, 3-4-dioxyephedrine, cobeprine, m-oxy-nor-ephedrine, and o-oxy-ephedrine used in this study. Paredrine and benzedrine were supplied by Smith, Kline & French Company, epinine by Burroughs Wellcome Company, neosynephrine by Frederick Stearns & Co., propadrine by Sharp & Dohme, Inc., and phenylethanolamine by Dr. Gordon Alles through the courtesy of Drs. Piness and Miller, of Los Angeles. The remaining compounds were the ordinary products obtained on the market.

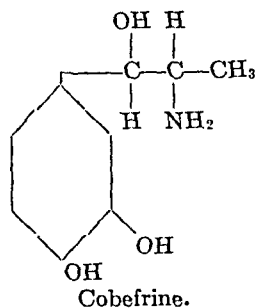
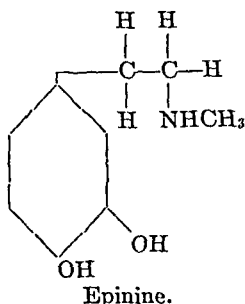
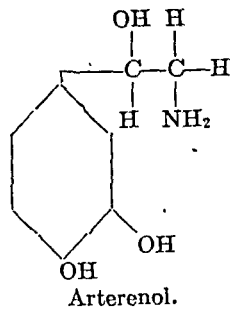
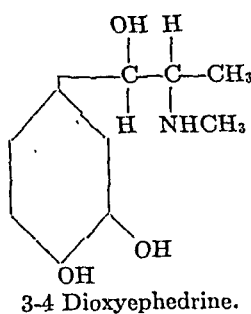
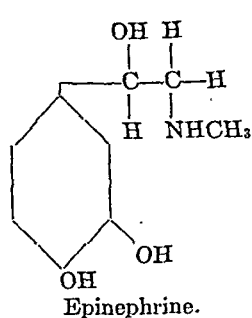


TABLE 1.—DOSES OF VARIOUS SYMPATHOMIMETIC AMINES REQUIRED TO RAISE BLOOD PRESSURE OF CATS TO A GIVEN LEVEL BEFORE AND AFTER PHENOL POISONING.*

Amine.	No. of cats used.	Phenol, mg. per kg. per min.	Doses of amine.		Ratio, $\frac{A}{B}$	Comparative ratios, Amine
			Before phenol (B) γ	After phenol (A) γ		
			Epinephrine			
Catechol-ring Derivatives.						
Epinephrine	32	2.6 (1.2-8.0)	3.3	5.1	1.4 (0.25-5.7)	1.0
Arterenol	11	2.6 (1.2-4.8)	6.8	10.0	1.2 (0.1-18.2)	0.86
3-4-dioxyephedrine . .	10	3.2 (1.9-4.0)	242.0	300.0	1.4 (0.22-2.3)	1.0
Epinine	10	2.0 (1.6-3.3)	50.0	56.0	2.3 (0.5- ∞)	1.6
Cobefrine	10	2.2 (2.1-2.7)	20.0	50.0	3.3 (1.5->10)	2.4
Median	1.4	1.0
Phenol-ring Derivatives.						
Paredrine	10	3.1 (1.2-3.7)	200.0	797.0	2.4 (0.43-15.9)	1.7
M-oxy-nor-ephedrine. .	10	2.6 (2.1-4.8)	100.0	200.0	3.0 (0.34->8)	2.1
O-oxy-ephedrine . .	5	2.6 (2.2-3.3)	390.0	2100.0	3.5 (0.93- ∞)	2.5
Neosynephrine . .	14	2.6 (2.0-3.5)	31.0	194.0	4.5 (0.59-59)	3.2
Tyramine	10	2.2 (1.0-4.0)	300.0	1000.0	5.9 (0.47- ∞)	4.1
Median	3.5	2.5
Phenyl-ring Derivatives.						
Phenylethanolamine . .	5	2.0 (1.9-3.3)	300.0	500.0- 2000.0	3.5 (0.44- ∞)	2.5
Propadrine	6	2.6 (2.0-3.3)	490.0	2880.0	5.8 (1800- ∞)	4.1
Benzedrine	5	2.6 (1.2-3.3)	67.0	300.0	6.0 (100- ∞)	4.3
Phenylethylamine . .	7	3.5 (2.3-4.8)	750.0	> 1000.0	∞	∞
Ephedrine	5	3.3 (2.0-4.0)	500.0	> 4800.0	∞	∞
Median	6.0	4.3

* The values in the table are medians with the ranges in parenthesis. The infinity signs signify that no rise or a fall of pressure was obtained with the highest doses used after phenol. The greater the numerical ratio in the last column, the lesser the pressor (antishock) efficiency of an amine.

improvement in the state of the circulation as result of the treatment with epinephrine.

Arterenol. This compound is interesting because it has been suggested as a possible hormone in the transmission of sympathetic nerve impulses, a possibility that has been explored by others. Chemically, it is an epinephrine-like molecule without the methyl radicle on the amino group, and thus it is somewhat simpler in composition than epinephrine. Arterenol was found to be effective in the same dosage range as epinephrine in stimulating the circulation both before and after phenol. Comparison of the doses in individual experiments showed that a median of only 1.2 times as large a dose was required after the phenol as before. Therefore, arterenol retained a greater pressor potency than did epinephrine. In other words, when the ratio of dosage before and after phenol was compared with that of epinephrine, it was only 0.86 times as large, which indicates an increase in efficiency of some 14% over that of epinephrine.

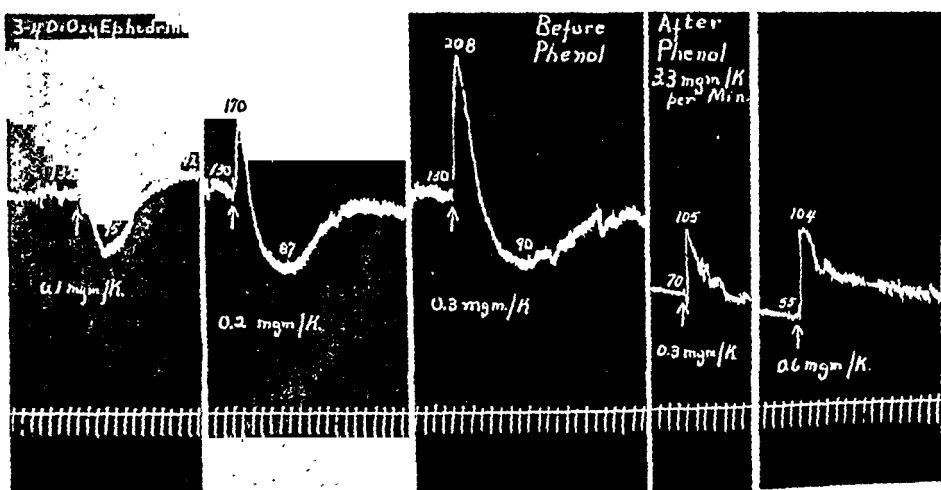


FIG. 1.—Effects of various doses of 3-4-dioxyephedrine in raising blood pressure, before and after phenol shock. Cat, urethane anesthesia. The time intervals are 30 seconds in all the figures. The numbers on the blood pressure tracing are the blood pressure in mm. Hg.

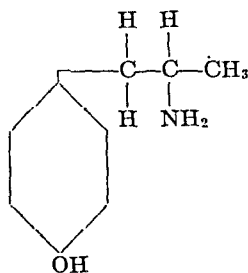
3-4 Dioxyephedrine. This compound resembles epinephrine except for the longer side chain. Therefore, it can be regarded as being intermediate between epinephrine and ethyl-nor-suprarenin, which one of us has recently shown to have interesting vasodilator actions.^{1,2} Although 3-4-dioxyephedrine has marked dilator power, in adequate doses it raised blood pressure very effectively. Typical effects are illustrated in Figure 1. After phenol, 300 gammas were required to produce the same pressor action as was obtained from a median of 242 gammas before the phenol. This made the ratio of dosage

1.4, which was the same as that for epinephrine. It was interesting that, after phenol, vasodilator actions appeared to be absent.

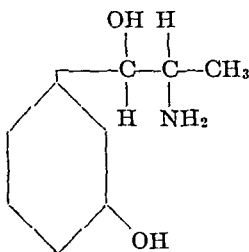
Epinine. This is another catechol which has some epinephrine-like actions, but with considerably diminished activity. Since about 2.3 times as much of this compound was required to raise the blood pressure after phenol as before, it was 1.6 times less active in maintaining its effect than was epinephrine.

Cobefrine. This compound has been introduced recently as a vasoconstrictor in local anesthesia. There was a considerable loss in its pressor activity after the phenol, as shown by an increase in dosage 3.3 times, in order to obtain the same percentage rise of pressure as before phenol. This meant that cobefrine was about 2.4 times less active than epinephrine for effective pressor action in phenol shock.

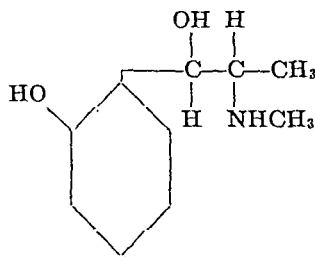
Phenol Ring Derivatives. The chemical composition and structure of the phenol ring derivatives used are illustrated by the following formulas:



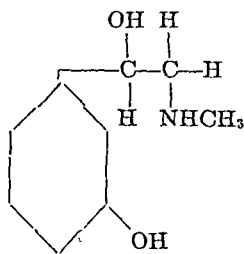
Paredrine.



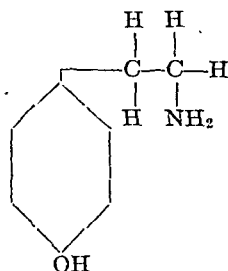
M-oxy-nor-ephedrine.



O-oxy-ephedrine.



Neosynephrine.



Tyramine.

Paredrine. This amine is a compound with a three carbon side chain, and a hydroxyl group in the para position of the aromatic ring. It has rather persistent pressor actions resembling those of ephedrine or neosynephrine rather than epinephrine. The dosage required was rather high, since 200 gammas was the median dose required for moderate pressor effects in the normal circulation. After phenol, paredrine lost a considerable part of its pressor activity, as shown by an increase in dosage of 2.4 times, in order to secure the same percentage rise as before phenol. This showed paredrine was 1.7 times less effective than epinephrine in recovering the low

blood pressure of phenol shock, at least as far as dosage required for equal pressor action was concerned. It was interesting to note, however, that an effective dose of paredrine kept the pressure elevated for an appreciably greater length of time than was the case with the other compounds studied.

Meta-oxy-nor-ephedrine. This is similar to paredrine, the only differences being a shift of the phenolic hydroxyl from the para to the meta position, and an alcoholic hydroxyl on the side chain. It showed a slightly worse maintenance of action on blood pressure after phenol than paredrine, since the dose had to be increased 3 times, which gave an action 2.1 times less well maintained than that of epinephrine.

Ortho-oxy-ephedrine. This amine is interesting mainly because it has its phenolic group in the ortho position. It had still less activity than the paredrine and meta-oxy-nor-ephedrine, since higher doses were required for pressor stimulation initially than with the others, and an increase of 3.5 times the control dose after phenol. This gave an action 2.5 times less well maintained than that of epinephrine under the same conditions.

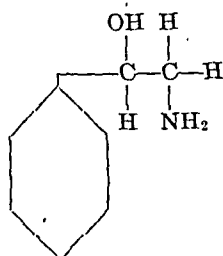
Neosynephrine. This epinephrine substitute has come into wide use as a vasoconstrictor in the nose and in local anesthetic solutions. Its pressor potency on the normal circulation was much greater than that of any of the other phenol ring derivatives, since only 31 gammas were required for the degree of stimulation used in this study. However, after phenol, this dose had to be increased a median of 4.5 times. Obviously it was much less effective in this type of circulatory collapse, than were the other compounds. However, interesting features of the neosynephrine action were the diphasic character of the responses of the normal circulation with a prolonged action, and persistent rise of pressure which it produced after phenol. In these respects, it behaved very much like paredrine and 3-4-dioxyephedrine.

Tyramine. This was one of the first amines to be studied and is the simplest, chemically, of the phenol ring compounds. Fairly large doses were required to stimulate the normal circulation, *i. e.*, a median of 300 gammas. After the phenol, it was difficult to produce any pressor effect at all, although equal percentage rises were produced when the dose was increased a median of 5.9 times. In some experiments, however, the largest possible doses of tyramine produced no increase in blood pressure after the phenol.

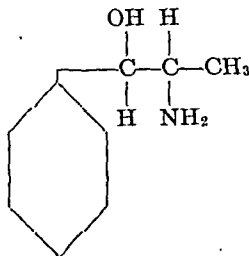
Phenyl Derivatives. The formulas on p. 803 indicate the chemical composition and structure of the phenyl derivatives used.

Phenylethanolamine. This amine behaved very much like the less active compounds in the phenol group, requiring an increase in dosage of 3.5 times. The same was true of *propadrine*, a compound which has been introduced recently as a vasoconstrictor for application in the nose. With both of these compounds, in two experiments

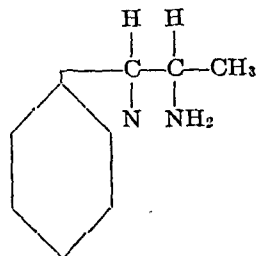
each, no rise of blood pressure could be produced in any dose after the phenol, indicating that the phenol effect seriously decreased their pressor potency.



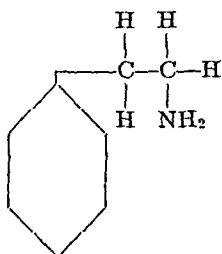
Phenylethanolamine.



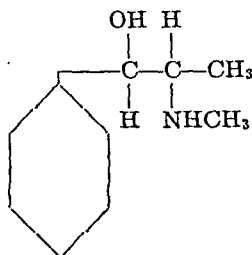
Propadrine.



Benzedrine.



Phenylethylamine.



Ephedrine.

Benzedrine. This compound has recently aroused new interest because of its powers to stimulate the central nervous system. It is also used as a vasoconstrictor in the nose, by inhalation of the vapors. Benzedrine was found to be the most effective pressor compound of the phenyl group for the normal circulation, requiring a median of only 67 gammas for stimulation. After phenol, however, great difficulties were experienced in getting any blood pressure responses whatever. The negative pressor effects of this otherwise rather stimulant compound are well illustrated in Figure 2. However, when the shock state was not too deep, some pressor response was obtained, but this required an increase in dosage 6 times that for the control response. This meant that benzedrine maintained its pressor action 4.3 times less well than did epinephrine.

Phenylethylamine. This is the simplest possible compound of the phenyl derivatives, being the skeleton structure with all the variable groups removed. It was extremely weak as a pressor agent for the normal circulation, since a median of 750 gammas were required, and was completely ineffective after phenol.

Ephedrine. This compound is used generally for such actions as raising blood pressure, constricting blood-vessels, and relaxing bronchial spasm. It is also used clinically to prevent or combat certain types of shock, as in spinal anesthesia. In our experiments, ephedrine had to be used in large doses to produce rises of blood pressure in the normal circulation, and after phenol, the pressor actions were practically completely lost. When the dose was in-

creased, after phenol, there resulted only a fall of blood pressure, which indicated a further circulatory depression if anything (Fig. 3). Accordingly, ephedrine was wholly ineffective in recovering the blood

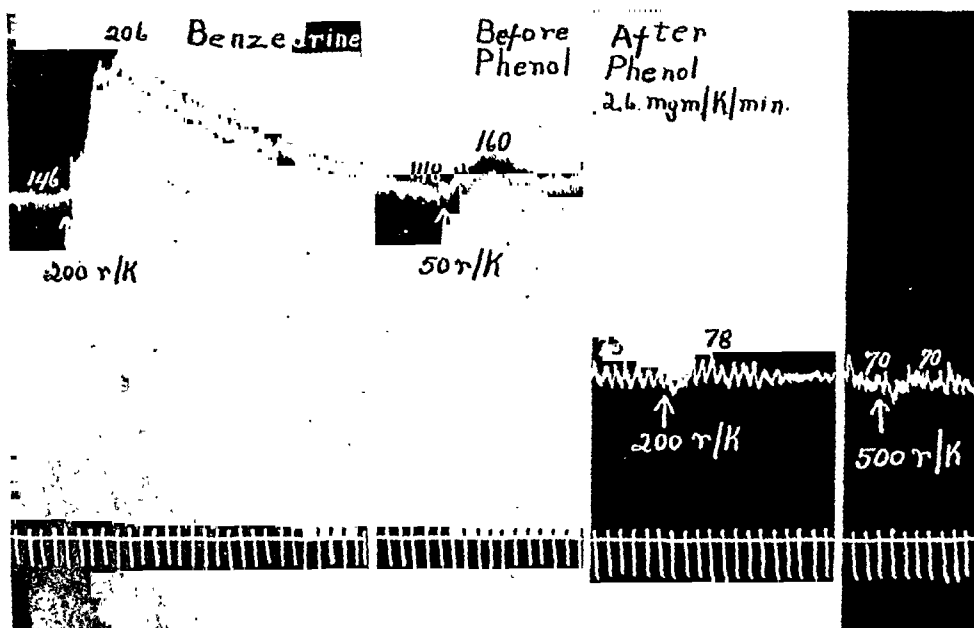


FIG. 2.—Effects of various doses of benzedrine in raising blood pressure before and after phenol shock. (Cat, urethane anesthesia.)

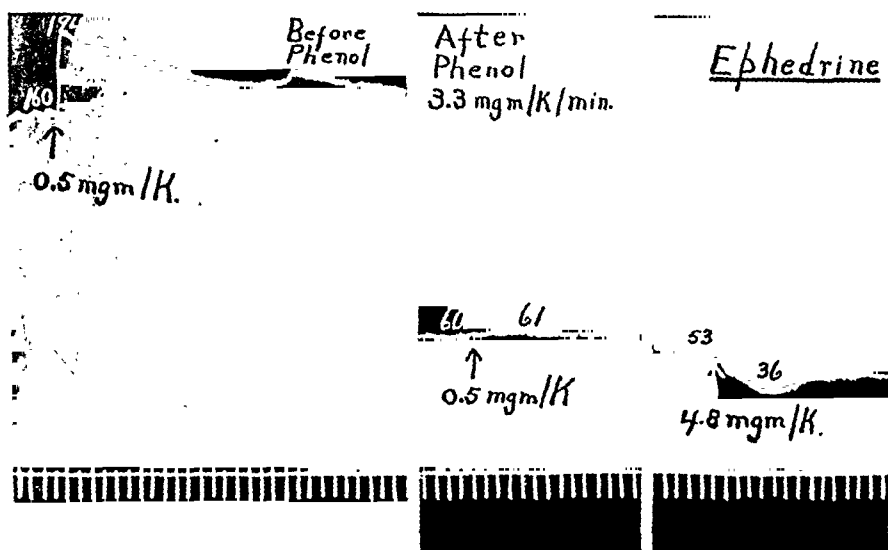
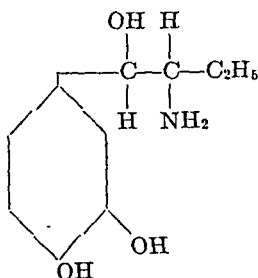


FIG. 3.—Effects of various doses of ephedrine in raising blood pressure before and after phenol shock. (Cat, urethane anesthesia.)

pressure in this kind of experimental shock at least. This failure was strongly in contrast with almost all the other agents studied.



Ethylnorsuprarenin.

Ethylnorsuprarenin has been studied previously by one of us^{1,2} as a compound with a very interesting mixture of vasodilator and vasoconstrictor actions. It was suggested in the previous papers, that it might be of value in certain conditions of circulatory failure since it would presumably stimulate the heart³ at the same time that it diminished the peripheral resistance.^{1,2} The typical vasodilator action was observed in the normal circulation, and, after phenol, there was still some vasodilatation present, as shown by further fall of blood pressure. Whether the circulation at this time was improved or not, so far as movement of total mass of blood per minute is concerned, could not be determined in the type of experiment employed. However, the observations have been recorded at this time for comparison with results on cardiac output to be determined in the future.

Comments. The results obtained in this study leave no doubt that the various sympathomimetic amines possess different degrees of pressor efficiency for the circulation depressed by phenol. From this it follows that these drugs should not be used indiscriminately, but only with due regard to their effectiveness under the circulatory conditions prevailing. In the experimental phenol shock used by us, the most effective compounds were the catechol ring derivatives, since their median activity was 1.4 as compared to a median value of 3.5 for the phenol ring derivatives. The phenyl compounds appeared to have little or no value in restoring the circulatory collapse of phenol poisoning, since, with many of these agents, no pressor effects could be produced. Some of these compounds even caused depressor effects, when attempts were made to increase the dosage to effective levels. Accordingly, it would appear that phenol very largely abolishes the response of the circulation to this group, and particularly to propadrine, benzedrine, and ephedrine, which might otherwise suggest themselves for clinical use in similar conditions.

If an attempt were made to explain the differences between these compounds according to other parts of their chemical structure than

the aromatic ring, a rather complete lack of correlation would be found. That is, there appears to be no consistent relationship between the presence of an ethyl or a propyl side chain, or between the presence or absence of an alcohol group on the side chain, or between the presence of a methyl-amino rather than the simple amino group, and the magnitude of the effects produced. These various linkages undoubtedly do affect the pressor responses to the compounds, but their individual influence is not great enough to determine a response in any consistent or distinctive manner. Of course, the same thing is true, but to a lesser degree, for the type of ring structure, since there is some overlapping in the activity observed in this study between the individual members of the groups of the three different rings. However, these ring structures cause enough differentiation of action that the effect of this part of the molecule is fairly evident.

TABLE 2.—SUMMARY OF DOSAGE RATIOS OF VARIOUS AMINES FOR PRESSOR EFFECTS, PERIPHERAL VASOCONSTRICTION, CARDIAC STIMULATION AND IN PHENOL SHOCK, IN TERMS OF EPINEPHRINE DOSAGE.

Compound.	Pressor. ¹	Peripheral vasoconstriction. ²	Cardiac stimulation. ³	Phenol shock. ⁴
Epinephrine	1.0	1.0	1.0	1.0
Arterenol	1.2	1.12	0.6	0.86
3-4-dioxyephedrine . .	41.0	31.4	1.5	1.0
Epinine	12.0	7.17	..	1.6
Cobefrine	3.3	2.48	0.23	2.4
Paredrine	295.0	33.4	3.8	1.7
M-oxy-nor-ephedrine . .	11.5	48.2	..	2.1
O-oxyephedrine	500.0	11.2	..	2.5
Neosynephrine	4.3	14.9	7.7	3.2
Tyramine	131.0	20.2	2.7	4.1
Phenylethanolamine . .	100.0	3.75	..	2.5
Propadrine	60.0	36.5	3.0	4.1
Benzedrine	425.0	dilator?	200.0	4.3
Ephedrine	350.0	72.1	21.3	..
Phenylethylamine . . .	183.0	6.08

¹ Pressor effects in normal cats.

² Vasoconstriction in perfused isolated legs of cats.

³ Cardiac stimulation in heart-lung preparation from cats.

⁴ Pressor effects in phenol poisoning compared with epinephrine (from Table 1).

An attempt was made to correlate the antishock (phenol) efficiency of these amines with efficiencies of other effects on the circulatory system according to the seat of action, with rather interesting results. Table 2 contains a summary of ratios for pressor effects on the intact normal circulation, obtained mainly from previous studies in this laboratory, vasoconstrictor effects in perfused cat leg vessels, quoted from a paper now in process of publication⁴ and cardiac effects in cat heart-lung preparations obtained from the study by Crismon and Tainter.³ All the values quoted in Table 2 are ratios of the magnitude of doses required to produce standard responses in proportion to effects in the same animal produced by moderate doses of epinephrine. Therefore, the higher the ratio the larger was the dose required, and the smaller the effectiveness of the amine, in

comparison with epinephrine under the same conditions. A comparison of the efficiencies under conditions of phenol shock and those of the three other circulatory states has been made according to the method of rank correlation.⁵ It was found that the correlation coefficient between the vasoconstrictor potency of the amines for leg vessels and their effects after phenol shock was only $+0.52$. When the correlation was made with their pressor ratios for the intact circulation, the coefficient increased to $+0.66$, thus indicating a closer correspondence between the effects in phenol shock and the total pressor efficiency in the intact organism than with the purely vascular actions. However, when the correlation was made with the ratios for the heart-lung preparation, then the unusually high coefficient of $+0.77$ was obtained, thus indicating a close correspondence between actions in phenol shock and on the heart directly. These correlations have an added significance, *i. e.*, they demonstrate that a circulation, which has been depressed by a cardiac depressant poison, is most effectively resuscitated by a drug which produces a high degree of cardiac stimulation rather than a vasoconstriction. The catechol compounds are very effective cardiac stimulants, as shown by the results on heart-lung preparations,³ and, therefore, they would be the agents of choice from among this group in the treatment of serious cardiac failure.

The result of this study, cannot, of course, be taken as definitive or exhaustive, in the sense that all the variables entering into circulatory responses to drugs in failure of the circulation have been considered, or that the kind of failure produced is representative of all. However, under the more or less arbitrary conditions used, differences between the closely related amines can be demonstrated, and these appear to be large or important enough to be clinically significant. Therefore, there has been provided an experimental basis for more rational treatment of circulatory failure of cardiac origin. The experimental data on the amines studied are incomplete in the sense that only the response of the blood pressure has been used as a measure of circulatory efficiency. It is by no means certain that this can give a completely adequate insight into the changes that may take place, since there should be known not only the changes in pressure of the blood, but also the effects on the rate of the flow and distribution, which may result from a treatment. Therefore, the studies here reported need to be supplemented by studies of cardiac output and of venous pressure, or, in other words, determinations of the state of compensation and efficiency of oxygenation of the tissues, so that these factors may also be considered before any final answer to the problem of treating circulatory collapse with drugs is formulated.

Conclusions. 1. The pressor efficiency of 16 sympathomimetic amines in the experimental shock of phenol has been determined in cats.

2. The catechol derivatives, namely, epinephrine, arterenol, 3-4-dioxyephedrine, epinine and cobefrine, preserved satisfactorily their pressor potency after phenol shock, since they required an increase in dosage of only from 1.2 to 3.3 times the control dosage in order to produce a given degree of pressor response.

3. The phenol ring compounds, namely, paredrine, meta-oxy-norephedrine, ortho-oxyephedrine, neosynephrine and tyramine, preserved their pressor potency moderately well, since the dosage had to be increased only from 2.4 to 5.9 times.

4. The phenyl ring compounds were almost completely ineffective in raising the low blood pressure of phenol shock, since small doses frequently caused no rise of pressure, and large doses tended to aggravate the collapse, if anything. Accordingly, phenol interfered with their stimulant power sufficiently to make them undesirable for use in treating circulatory failure from this cause, at least.

5. Consideration of the pressor potency alone of sympathomimetic amines is not sufficient to provide a satisfactory basis for selection of these agents as circulatory stimulants in shock, since, when the heart is depressed, the cardiac stimulant drugs are more effective than are agents whose preponderant action is on the peripheral vessels. Rational treatment of acute circulatory failure necessitates an understanding of the cause or causes of the failure, in order that entirely successful drugs or measures may be used.

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INTERMITTENT VENOUS COMPRESSION IN THE TREATMENT OF PERIPHERAL VASCULAR DISORDERS.

A REPORT ON 103 CASES.

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AMONG the more recent methods of treating vascular diseases, is periodic venous compression advocated by Collens and Wilensky.¹ The principle of this method is not new. Bier² was impressed by nature's attempt to overcome inflammation and trauma by a resulting hyperemia which develops. He decided that it may be beneficial to induce vasodilatation by constricting the larger vessels, "thereby increasing the beneficent hyperemia resulting from the fight of the living body against the invasion."

Lewis and Grant⁷ investigated the effects of occlusion of the larger vessels. They observed that a state of vasodilatation follows the period of compression of the arteries and that this reaction is in proportion to the period of occlusion. They termed this vasodilatation stage as reactive hyperemia and attributed its development along two lines: first, the tissue metabolites which accumulate in the tissues when blood flow is arrested (these substances presumably possess a vasodilator action upon the smaller vessels); second, the discharge of the accumulated "blood flow debt." Other factors, such as the influence of an increase in venous pressure and the mechanical effect of the filling and stretching of the venules and capillaries, resulting from periodic venous compression, have been emphasized by de Takats³ and his associates.

Cushing,² in 1902, advocated the tourniquet as a means of treating and overcoming the vasospasm in Raynaud's disease. Jordan,⁴ in 1935, employed similar measures with elevation of the leg and constricting the thigh by inflating an ordinary sphygmomanometer cuff and then releasing the air.

In 1936, Collens and Wilensky devised an apparatus, electrically controlled, which would produce obstruction of the venous return in the extremities, alternating with periods of release. The description of this apparatus and the details of its technique can be found in their publications. The pressure usually employed varies from 40 mm. to 80 mm. of mercury. The optimum pressure for results is in the higher ranges: about 80 mm. mercury. Treatments, for active cases, vary from 1 to 2 hours daily or in some cases the treatment is continued for 24 hours or longer, depending upon the response and reaction of the patient.

Results. This method was employed on a series of 103 patients: most of them were treated in the office and Vascular Clinic, a smaller number were bed-ridden. Many of these patients had received other forms of therapy previously, in some the treatment was combined with additional measures, in others the reactive hyperemia was the only form of treatment. For convenience, the series of patients are arranged in disease groups and the effects of the treatment upon the symptoms and the disease may be noted from the following tables.

Diabetes. There were 24 diabetic patients complaining of symptoms indicating an impaired peripheral circulation and confirmed by circulatory function tests. These patients varied in age from 48 to 75 with one exception, a boy of 15, who had diabetes of 4 months' duration. He subsequently complained of fatigue and coldness of the legs and showed a clinical picture of a slightly impaired circulation.

Seven of the patients had gangrene and 2 had ulcers. In this series, 12 were definitely improved as evidenced by (a) the subsidence of symptoms, (b) clinical improvement, such as the healing

of ulcers or (c) checking the threatened or impending gangrene. Four showed some improvement; in 2 cases, there was temporary improvement; in 6 others, none at all. Of the 9 more serious cases who had a gangrenous lesion or threatened gangrene, 5 obtained good results. Some of the results were most gratifying, as in the patient A.H. (Case 10), where the toe had been amputated and where the impairment of circulation was in evidence at the time of the operation by the lack of bleeding. Later an ulcer developed, extending along the outer aspect of the foot, exposing a considerable area of the 5th metatarsal. This was attended with severe pain and suffering. After 48 hours of treatment, there was a subsidence of symptoms, and after a prolonged convalescence the patient made an excellent recovery.

TABLE 1.—EFFECT OF REACTIVE HYPEREMIA UPON DIABETICS.

Case.	Name.	Age.	Sex.	Duration, yrs.	No. treatments.	Improvement of symptoms.						General improvement.				Other treatment; remarks.	
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temp.	None.		
						Yes.	No.	Yes.	No.	Yes.	No.						
1	I. A.	58	M	2	3	x	x	..	x	Pavaex mecholyl.	
2	G. E.	65	F	..	12	x	..	x	..	x	..	x	
3	W. F.	48	F	3	7	x	..	x	..	x	..	x	
4	C. F.	59	F	2	15	..	x	..	x	..	x	x	
5	A. W.	65	M	8	20	x	..	x	Mecholyl.	
6	M. M.	60	F	..	21	x	..	x	..	x	Mecholyl.	
7	E. R.	70	F	4 mos.	3	x	..	x	x	Mecholyl.	
8	L. B.	56	F	3	35	..	x	..	x	..	x	x	Pavaex; died.	
9	L. G.	49	M	11	10	..	x	x	..	x	..	x	x	Transverse myelitis.	
10	A. H.	75	M	1	32	x	..	x	..	x	..	x	Ulcer healed.	
11	J. S.	64	M	2	32	x	..	x	..	x	..	x	
12	H. C.	65	F	2	x	..	x	
13	M. N.	55	M	5 wks.	30	x	..	
14	S. C.	64	F	2 mos.	10	x	x	Gangrene; died.	
15	M. D.	57	M	2	8	x	x	Neurologic.	
16	M. S.	52	F	8 mos.	12	x	..	x	..	x	x	Traumatic arthritis.	
17	J. M.	64	M	1	40	x	..	x	..	x	3 toes removed; gangrene controlled.	
18	R. S.	51	F	15	15	†	x	
19	F. D.	60	F	5	8	..	x	x	..	x	..	x	
20	M. G.	55	F	4	8	x	..	x	..	x	..	x	
21	L. E.	63	F	3	14	x	x	x	..	Later, amputation.	
22	H. K.	15	M	4 mos.	5	x	x	
23	H. W.	69	M	2 wks.	50	x	x	One leg amputated.	
24	H. A. W.	56	M	6 mos.	10	x	x	Ulcer.	
Totals:						..	8	5	14	3	10	9	12	4	2	6	

* Patient died. Diabetic gangrene, gas bacillus.

† Gangrene ulcer healed.

In Case 17 (J.M.) gangrene was finally controlled after three toes had been removed, but an open ulcerative wound persisted. He ultimately responded to treatment with complete recovery. This was an unusual result, because amputation was considered in two different institutions.

In Case 23 (H.W.) male, after one leg was amputated, he had threatened gangrene of the other foot involving the heel. The

circulation was improved by a series of treatments and the condition was finally checked.

Of the 6 failures, 2 (Cases 13 and 14) had rapidly developing gangrene which could not be controlled and 2 others (Cases 7 and 8) had evidence of extensive lesions in the vessels and could not be benefited by treatment. One of the other failures had a transverse myelitis, where the symptoms were most likely produced by a neurologic disturbance rather than vascular disease. The remaining case (24) had extensive ulceration of the leg, complicated with a staphylococcus infection, which failed to respond to treatment.

TABLE 2.—EFFECT OF REACTIVE HYPEREMIA UPON BUERGER'S DISEASE.

Case.	Name.	Age.	Sex.	Duration, yrs.	No. treatments.	Improvement of symptoms.						General improvement.				Other treatment; remarks.
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temp.	None.	
						Yes.	No.	Yes.	No.	Yes.	No.					
1	E. B.	33	M	3	3	..	x	x	..	x	..	x	Mecholyl.	
2	J. B.	62	M	...	37	x	..	x	..	x		
3	H. E.	43	M	3	2	x	x	..	x		
4	H. M.	33	M	4	7	x	..	x	Pavaex mecholyl.	
5	J. G.	63	M	3	30	x	..	x	Mecholyl.	
6	E. G.	45	M	15	4	x	x	x		
7	H. P.	57	M	...	4	x	x		
8	S. B.	20	M	3	12	x	x	Mecholyl pavaex.	
9	M. M.	54	M	1	30	x	..	x	..	x	..	x	Pavaex; threatened gangrene.	
10	H. E.	39	M	3	40	x	..	x	..	x	x	..	Oscillometer; showed improvement.	
11	S. J.	45	M	2	22	x	..	x	x	..	Ganglionectomy.	
12	H. R.	55	M	5	7	..	x	x	x	x	Na. citrate.	
13	N. G.	43	M	2	7	x	x	x	..	Vaccine.	
14	F. C.	60	M	3	14	x	..	x	x		
15	F. S.	50	M	2	6	x	..	x	x	
16	M. B.	31	M	2	11	x	..	x	..	x	..	x	Mecholyl.	
17	P. C.	72	M	10	4	x	..	x	x	..		
18	F. R.	45	M	1	8	x	x	..		
19	W. B.	62	M	6	8	x	..	x	..	x	..	x	Mecholyl.	
20	F. K.	52	M	6 mos.	9	x	..	x	..	x	Mecholyl.	
21	J. D.	55	M	2 mos.	14	x	..	x	..	x	x	..	Pavaex.	
Totals:					..	10	2	18	1	14	4	6	8	3	4	

Thromboangiitis Obliterans. Twenty-one patients with Buerger's disease were observed. In 6 of these, good results were obtained, while 8 patients showed some improvement. Three others indicated temporary improvement and the remaining 4 were not benefited by the treatment. This gives a total of 14 patients (66.6%) who either had good results or showed some improvement. But we cannot attribute the improvement entirely to this form of therapy, because we must take into consideration the fact that practically all of these patients had some other form of treatment as well. In this respect, our experience coincides with that of others who have occasion to treat this group of unfortunates. We cannot resist the temptation of combining various methods of treatment in order to

obtain more prompt results. This factor seems to be a recognized barrier when attempting to evaluate the merits of any one form of therapy.

Arteriosclerosis. In the arteriosclerotic group, 15 patients were treated. Four had good results, 5 showed some improvement, 2 were temporarily improved, while in the other 4 cases no improvement was noted.

TABLE 3.—EFFECT OF REACTIVE HYPEREMIA UPON ARTERIOSCLEROSIS.

Case.	Name.	Age.	Sex.	Duration, yrs.	No. treatments.	Improvement of symptoms.						General improvement.				Other treatment; remarks.
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temp.	None.	
						Yes.	No.	Yes.	No.	Yes.	No.					
1	S. C.	69	M	9 wks.	14	x	..	x	x	..	x	Pavaex.
2	E. S.	64	M	7 mos.	30	x	..	x	x	..	Cellulitis controlled
3	S. M.	68	F	8	6	x	x	..	x	..	x	Sod. cit.; embolic.
4	G. C.	52	M	6	7	x	x	..	x	..	x	
5	A. B.	57	M	4	12	..	x	x	x	..	x	Pavaex.
6	E. D.	69	M	5	7	x	..	x	x	x	
7	Z. R.	76	M	2	20	x	..	x	..	x	..	x	Pavaex.
8	L. T.	72	M	5	12	..	x	..	x	..	x	x	Mecholyl.
9	H. L.	58	M	3	13	x	..	x	x	
10	A. M.	69	F	6	30	x	..	x	..	x	..	x	Sod. cit.; gangrene delayed.
11	L. W.	68	M	2 mos.	*	Embo lic occlu sion						x	..	Mecholyl.
12	A. P.	63	M	2	17	x	..	x	..	x	..	x	Sod. cit.; gangrene delayed.
13	S. S.	55	M	6 mos.	8	..	x	x	x	x	Mecholyl.
14	E. P.	53	M	1½	19	x	..	x	Trophic ulcer.
15	A. Z.	63	M	2 mos.	12	x	..	x	..	x	
Totals:					..	8	3	11	3	6	7	4	5	2	4	

* Daily.

There were some instances where we felt the treatments accomplished gratifying results. Case 4, with an embolic occlusion in one of the smaller branches of the leg was benefited. Case 10 showed evidence of a markedly impaired circulation of both extremities, with distress. The symptoms responded nicely to treatment. However, this patient also had received mecholyl by iontophoresis. Case 11 had occlusion of one of the large branches of the popliteal. He was given an intensive course of treatment, gangrene was delayed for 4 weeks but ultimately the limb had to be removed. Case 15 had a distressing trophic lesion. This patient responded to therapy with the healing of the lesion and not only were the symptoms controlled but the progressiveness of the vascular occlusion was evidently checked.

Phlebitis. In this group, 33 patients received treatment. They ranged from acute and migrating forms of infectious phlebitis to the subacute and chronic type.

In Table 4 one may note the frequency of cramps which occurred in these patients. This suggests some relationship of phlebitis upon

the accompanying arteries, most likely in the form of vasospasm. The circulatory function tests showed that there was some impairment of circulation in this group. Probably this explains the beneficial effects of either mecholyl by iontophoresis or periodic venous occlusion or their combination.

TABLE 4.—EFFECT OF REACTIVE HYPEREMIA UPON PHLEBITIS.

Case.	Name.	Age.	Sex.	Duration, yrs.	No. treatments.	Improvement of symptoms.						General improvement.				Other treatment; remarks.
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temp.	None.	
						Yes.	No.	Yes.	No.	Yes.	No.					
1	D. K.	34	F	10	32	x	x	x	..	Mecholyl.
2	H. K.	38	M	1	5	x	..	x	..	x	x	Pavaex.
3	H. O.	30	M	6	16	x	x	Local.
4	E. H.	54	M	1	5	x	x	..	
5	E. T.	28	F	7	20	x	..	x	x	Eczema improved.
6	B. L.	45	F	6 mos.	20	x	..	x	..	x	x	Mecholyl; vasospasm.
7	S. B.	39	F	3	12	?	..	x	x	..	Pregl's.
8	W. C.	52	F	5	9	..	x	x	..	x	x	Pregl's.
9	A. C.	51	M	7	9	x	..	x	..	x	..	x	Tissue ex.
10	C. F.	55	F	6	5	x	x	x	x	Vaccine.
11	P. G.	47	M	5	12	..	x	x	x	x	..	Vaccine.
12	A. O.	30	F	4	6	x	x	x	..	x	Vaccine.
13	G. A.	47	M	8	10	x	x	x	..	x	
14	E. S.	48	F	7	30	x	..	x	..	x	Vaccine.
15	C. B.	50	M	2	20	x	..	x	..	x	Pregl's; acute phlebitis subsides.
16	C. E.	42	F	16	28	x	..	x	..	x	..	x	Mecholyl.
17	O. G.	49	M	4	18	x	..	x	..	x	..	x	Mecholyl; phlebitis, acute.
18	J. M.	21	M	3 mos.	14	x	..	x	..	x	..	x	Mecholyl—Pregl's.
19	A. K.	44	M	4	8	x	..	x	x	..	x	Mecholyl, prontoslin; open ulcer.
20	C. N.	39	F	1	8	x	..	x	..	x	..	x	Mecholyl.
21	R. C.	63	F	6 mos.	14	x	..	x	x	..	x	Mecholyl; marked stiffness.
22	M. F.	31	M	5	37	x	..	x	..	x	..	x	Mecholyl; migrating phlebitis.
23	O. H.	30	F	4	5	x	x	Mecholyl.
24	B. C.	34	M	3	x	..	x	..	x	x	
25	F. C.	53	F	1	25	x	..	x	x	..	Vaccine.
26	E. P.	68	M	8	4	x	..	x	..	x	x	
27	H. C.	66	M	1	8	x	x	
28	H. S.	44	F	10	17	..	x	..	x	x	x	Pregl's.
29	A. G.	51	F	15	11	x	..	x	x	..	
30	R. H.	23	F	6	17	x	..	x	..	x	Mecholyl; swelling subsided.
31	M. A.	37	F	6 mos.	16	x	..	x	..	x	..	x	Mecholyl.
32	M. E.	29	M	4	12	x	..	x	..	x	..	x	Pregl's sol.
33	P. W.	40	M	4 mos.	14	x	..	x	..	x	..	x	
Totals:					..	19	4	23	5	25	5	16	8	7	2	

Miscellaneous Group. In this series, there were 4 cases of ulcer, 3 of which had been treated unsuccessfully over a long period. With reactive hyperemia, good results were obtained in Cases 7 and 8, and a fairly good result was recorded in Case 10. In Case 2, there was a temporary improvement, but the patient subsequently was found to have osteomyelitis of the metatarsal and was referred to the surgeon for proper care. Another patient (Case 9), female, complained of coldness of the hands and feet. She was not affected by the treatment. This patient presumably had vasoneurosis and

was not benefited by the short series of treatments she had received. Case 4 had an embolic occlusion of one of the peroneal branches. The patient was temporarily improved and recorded as such. Circulatory function tests showed definite improvement in the circulation of the extremities.

TABLE 5.—EFFECT OF REACTIVE HYPEREMIA—MISCELLANEOUS.

Case.	Name.	Age.	Sex.	Duration, yrs.	No. treatments.	Improvement of symptoms.						General improvement.				Other treatment; remarks.	
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temp.	None.		
						Yes.	No.	Yes.	No.	Yes.	No.						
1	E. W.	44	F	1	10	x	..	x	x	Mecholyl; arthritis.	
2	L. N.	34	F	5	3	x	..	x	..	x	x	Pavaex; osteomyelitis.	
3	E. F.	57	F	7	14	x	x	Arthritis.	
4	C. P.	48	M	5 mos.	44	..	x	x	x	Pavaex mecholyl.	
5	H. Y.	33	M	3	12	x	..	x	..	x	..	x	Vasospasm.	
6	B. S.	45	M	4	7	x	x	..	x	Vaccine.	
7	J. L.	56	M	7	14	Healed	
8	E. W.	35	M	4	11	x	x	Trophic ulcer.	
9	B. McG.	46	F	5	4	x	Vasoneurosis.	
10	B. K.	50	M	3	9	x	..	x	..	x	x	Trophic ulcer.	
Totals:						..	5	1	5	..	7	..	4	3	2	1	

TABLE 6.—AN ANALYSIS OF THE EFFECT OF PERIODIC VENOUS COMPRESSION UPON SYMPTOMS AND DISEASE GROUPS, IN 103 CASES.

Disease group.	No. cases.	Symptoms improved.						Results.				Total.	
		Cramps.		Fatigue.		Pain.		Good.	Some.	Temp.	None.	Benefited.*	Unimproved.†
		Yes.	No.	Yes.	No.	Yes.	No.						
Diabetes	24	8	5	14	3	10	9	12	4	2	6	16 (66.6%)	8 (33.3%)
Buerger's disease	21	10	2	18	1	14	4	6	8	3	4	14 (66.6%)	4 (33.3%)
Arteriosclerosis	15	8	3	11	3	6	7	4	5	2	4	9 (60%)	6 (40%)
Phlebitis	33	19	4	23	5	25	5	16	8	7	2	24 (72.8%)	9 (27.2%)
Miscellaneous	10	5	1	5	..	7	..	4	3	2	1	7 (70%)	3 (30%)
Totals . . .	103	50	15	71	12	62	25	42	28	16	17		
Percentages	...	77	23	85.6	14.4	71.3	28.7						

* Total benefited—include those with some improvement.

† Temporarily improved—included with the failures.

Among the others, there were 2 cases of arthritis, of which 1 showed improvement; and 2 patients with vasospastic disorders. In both of these, good results were obtained.

Effect of Reactive Hyperemia Upon Symptoms. The results of periodic venous occlusion upon the symptoms in the various diseases have been tabulated and arranged in Table 6. The best results were obtained in relieving fatigue, 71 patients out of 83 (85%) admitting improvement. The next best was its influence upon

cramps, 50 out of 65 patients (77%) showing a decided improvement, and upon pain, 62 out of 87 (71%) being relieved.

We were somewhat surprised to note the favorable influence upon the symptoms in thromboangiitis obliterans, and the disappointing percentages of the diabetic group. Whether or not this has any significance is a question which cannot be discussed at this time. The failure to respond to pain is understandable, because of the tendency of diabetics to develop neuritis; but we notice the high percentage of failures to relieve pain in the arteriosclerotic group, as well. Nevertheless, in isolated cases, we have seen patients suffering from excruciating pain respond to intermittent venous compression.

The gratifying effects upon fatigue and cramps presumably involve the tissue metabolites or other vasodilator substances and some beneficial effect upon tissue metabolism. Collectively, this form of therapy gives us an average of 78% favorable influence upon symptoms, a result which we think is commendable. It would be interesting to compare these percentages with statistics of other forms of treatment. This we hope to present for publication in the near future.

The summing up of the results of periodic venous compression upon the disease groups was somewhat more difficult. The decision was made not only upon the patient's response to symptoms, but upon physical findings and circulatory function tests as well. If the patient insisted he was not better despite some evidence of changes in his condition, he was recorded as a failure. On the other hand, if he stated that he was considerably improved, but complete evidence of this improvement was lacking, he was listed as somewhat improved. In some cases, there was a tendency for the author to "lean backwards" when final results were registered, particularly in the group of thromboangiitis obliterans.

The diabetic and Buerger's disease groups showed 66.6% were benefited. For the latter disease, these figures would rate as average because of the pathologic state of the vessels. No one form of therapy gives uniformly good results in thromboangiitis obliterans, with the possible exception of surgery and, even with this method of treatment, the cases must be selected. In the diabetics, we got better results with mecholy by iontophoresis. This was reported in a previous publication⁶ and, although the figures were based on a small series at that time, we still are inclined to believe that a study of a larger number would confirm our original deductions.

The arteriosclerotic group was disappointing, giving the lowest percentage (60%) of those who were benefited. We cannot explain this finding, unless the arteries were too extensively involved and the tissues incapable of responding satisfactorily.

The phlebitis series, on the other hand, showed a surprisingly high percentage, 72.8. This is gratifying when we consider the difficulties encountered in treating this type of vascular disease.

The favorable results can be attributed to: (1) the frequency of vasospasm associated with the phlebitis; and (2) the combined therapy which was given to a majority of these patients. Some of them received mecholyl by iontophoresis, which has already been accredited^{5,9} as a successful form of treatment in phlebitis and varicose ulcers. It may be pertinent to mention that these cases must be treated cautiously. Phlebitis is a recognized contra-indication to the use of negative-positive pressure exercises. With intermittent venous compression, we would suggest that low pressure, 35 to 40 mm., be employed in the beginning and short treatments of 20 to 30 minutes during the active stages. The pressure may be gradually increased and treatments prolonged, as the condition improves. This applies to the subacute and chronic forms. Acute cases of phlebitis with extensive involvement and high temperature were not included.

The fifth group of miscellaneous conditions will not be discussed in detail since the series is small and were included only because they showed some possibility of having a vascular disorder. No attempt was made to select cases when these investigative studies were undertaken.

Summary and Conclusions. Periodic venous compression is offered as another method in treatment of peripheral vascular diseases. It is based on logical principles and investigations have shown that it does produce a beneficial effect upon the circulation.

A series of 103 patients were observed, totalling about 1500 treatments. The usual run of vascular disorders were included, except the vasoneuroses and Raynaud's disease groups.

The results upon Buerger's disease and diabetics were average, 66.6% being benefited. The arteriosclerotic group was disappointing, favorable results being obtained in only 60%.

Phlebitis constituted the largest series, with 33 patients. Vasospasm was a common occurrence in these cases. The analysis showed that 72.8% were favorably influenced.

Collectively, 70 patients (68%) of the 103 in the series were benefited. Because of its favorable influence upon various vascular disturbances and because of its broader application, we consider intermittent venous compression a desirable addition and adjunct in the treatment of peripheral vascular diseases.

We wish gratefully to acknowledge the coöperation of the Surgical and Medical Departments and the privilege of observing their patients in this investigation.

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HERPES ZOSTER AND ITS VISCERAL MANIFESTATIONS.

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IN view of the fact that herpes zoster can produce a subjective symptomatology simulating organic disease, we have summarized a series of cases admitted to a large general hospital together with a smaller number from private practice.

During the 10-year period between 1925 and 1935 there were 131 patients discharged from the wards of Bellevue Hospital with a diagnosis of herpes zoster. During this time there was a total admission of approximately 200,000 cases. To these 131 are added 6 cases from private practice. This group comprises only primary cases of herpes zoster. Those instances of zona arising as a secondary manifestation, during the course of another disease such as Hodgkin's disease, lymphomas, neoplasms, lues, and so forth, and zona of the cranial nerve ganglia have been excluded. It must be noted that this group of patients were ill enough to require hospitalization or presented a confusing symptomatology. Otherwise they would have been treated in the out-patient department, as is the usual practice with herpes zoster.

The average age of the patients is 51.7 years, the youngest being 19, the oldest 76. The sex incidence is 3 males to 2 females.

The predominance of pain as an initial symptom is striking, being present in 118 cases. In 86, the pain preceded the rash by an average of 6.4 days. In 5, pain and rash occurred simultaneously and in the remainder the time relationship was not noted.

The chief initial complaint in the 19 remaining cases was rash, malaise, headache, dyspnea, palpitation, nausea, anorexia and diarrhea occurring in the frequency given, with pain a secondary symptom (Table 1). In 41 cases an upper respiratory infection preceded or accompanied the initial complaint. Of these, there were 6 cases of pleurisy, 3 with bronchitis and 3 with bronchopneumonia. Four cases had severe chills. In only 18 cases did the temperature rise over 100° F. for 2 successive days. The hemoglobin and blood counts were normal. The leukocyte count was never above 10,000 and usually ranged from 5000 to 7000, the differential remaining consistently normal, excepting in the 1 instance noted below.

The spinal fluid was examined in 11 instances. In 6 it was normal and in the remaining 5 there was an increase in the cell count rang-

ing from 40 to 110 cells per c.mm. of which from 90 to 95% were lymphocytes. Globulin was found in 4 cases. Two of the patients with a pleiocytosis had varicella as well as herpes zoster. The Wassermann reaction was negative in all.

TABLE 1.—SHOWING THE PREDOMINANT INITIAL SYMPTOM IN EACH CASE AND THE LOCATION OF THE SKIN LESION WHEN THE EXACT DISTRIBUTION WAS NOTED.

<i>Pain as Predominant Initial Symptom.</i>						
<i>Location of Pain in 118 Cases.</i>				<i>Location of Skin Lesion When Exact Distribution Was Noted.</i>		<i>Cases.</i>
Head . . .	5	Rt. head . .	2	Cervical . . .	1	1
		Lt. head . .	3		2	1
Face . . .	3	Rt. face . .	3		3	1
Neck . . .	2	Rt. neck . .	2		4	3
Eye . . .	5	Lt. eye . .	2		5	2
		Rt. eye . .	3		8	2
Chest . . .	37	Rt. chest . .	13	Accessory sp. nerve		1
		Lt. chest . .	24	Thoracic . . .	1	2
Breast . . .	2	Rt. breast . .	1		3	1
		Lt. breast . .	1		4	3
Precordium . .	4				5	4
Abdomen . .	34	Lt. abdomen .	6		6	3
		Rt. abdomen .	10		7	2
		R.U.Q. . .	6		8	5
		L.U.Q. . .	5		9	5
		R.L.Q. . .	3		10	11
		L.L.Q. . .	1		11	11
		Epigastric . .	3		12	11
Lumbar . . .	6	Rt. lumbar . .	2	Lumbar . . .	1	3
		Lt. lumbar . .	4		2	3
Groin . . .	2	Rt. groin . .	1		4	1
		Lt. groin . .	1		5	1
Back . . .	5				6	1
Extremities . .	13	Lt. shoulder and arm . .	3	<i>Remainder of Distribution Noted Only by Locality.</i>		
		Rt. shoulder and arm . .	8	About umbilicus		4
		Rt. foot . .	1	On chest		18
		Rt. hip . .	1	Back		2
<i>Initial Symptoms Other Than Pain.</i>				Lumbar region		1
Dyspnea . . .	1			Buttock		1
Palpitation . .	1			Leg		1
Severe general headache . .	5			Forehead		15
Nausea . . .	1			Face		7
Anorexia . . .	1			Soft palate		2
Attacks of unconscious . .	1			Abdomen		5
Gen. malaise . .	2			Arm		5
Rash . . .	6			Thigh		2
Diarrhea . . .	1			Shoulder		4
Total cases . .	137			Neck		3
				Ear		1
				Foot		3

Recurrence was noted in 8 cases, occurring annually in 1. The longest interval between attacks was 20 years.

Bilateral herpes zoster was noted only once.

Adenopathy, although usually described as being frequently present, was pronounced in only 6 cases. It sometimes occurred

prior to the skin lesion. In 3 of these there was a secondary skin infection and 2 were associated with a generalized lesion diagnosed as varicella.

It is of definite interest to consider 3 cases in our series in which varicella-like lesions were found concomitant with herpes zoster. These cases were more acutely ill and their course more protracted. The zoster lesions were more numerous and extensive, and in 2 of the cases gangrenous and necrotic lesions appeared. Small vesicles involving the mucous membrane of the cheek, pharynx, uvula and hard palate were found in all 3 instances. The 2 cases in which the spinal fluid was examined showed pleiocytosis and 1 of the patients developed an encephalomyelitis from which she recovered (see below).

In all, derangements of the central nervous system were found in 7 cases, during and following the disease. These were 3 instances of post-herpetic neuralgia, 1 case of post-herpetic anesthesia, 2 of post-herpetic lower motor neuron paralysis of the anterior abdominal muscles with herniation and 1 case of encephalomyelitis.

CASE 1.—This latter was a female patient of 48 years who complained of pain of a week's duration in the right chest, the right lumbar region and the right hip. Examination showed a typical herpes zoster at the level of the lower angle of the right scapula, associated with epigastric pain and tenderness. There were small varicella-like vesicles on the forehead, soft palate, shoulder, right abdomen and hip. Some of the herpetic vesicles were gangrenous. Neurologically there were bilateral Babinski, positive Brudzinski, bilateral Gordon-Oppenheim reflexes and absent abdominal reflexes. The spinal fluid showed 75 cells, 95% of which were lymphocytes, 1+ globulin and 3+ sugar. A diagnosis of varicella, encephalomyelitis, posterior ganglionitis and herpes zoster was made. The patient was discharged as completely cured after 11 days at the hospital.

CASE 2. One of the cases with post-herpetic lower motor neuron paralysis was a 55-year-old man, whose chief complaint was a severe and intractable pain radiating from the right costovertebral region to the right loin. There were typical varicella-like lesions scattered over the entire forehead, trunk and hard and soft palate. He presented a typical herpes zoster along the distribution of the right 11th and 12th thoracic and 1st lumbar nerve. The pain persisted for several weeks. During this time he noted a bulging of his right lower abdominal wall. This was found to be due to paralysis of the lower portion of the right rectus and external oblique muscles. The lower abdominal reflex was absent on that side. The abdominal weakness has persisted, almost unchanged, giving him a distinct bulge in this region, but the pain has disappeared and there are no sensory residua. Masten²¹ cites a similar case.

Another feature of the disease that may lead to an error in diagnosis is the appearance of a fiery red erythema, extending for a wide area about the vesicles. This led to an admission diagnosis of erysipelas in 6 instances, 3 of which received erysipelas antitoxin.

Since our primary interest concerns itself with 42 cases in which there were symptoms referable to the viscera (Table 2) special note will be made of this group. In 38 the visceral symptomatology so

TABLE 2.—CASES IN WHICH THERE WERE SYMPTOMS REFERABLE TO THE VISCERA WITH PRESENTING SIGN, ADDITIONAL SIGNS AND SYMPTOMS, MISTAKES IN ADMISSION DIAGNOSES, LABORATORY EXAMINATIONS AND LOCATION OF SKIN LESION.

42 cases with visceral symptoms.		Presenting signs.		Additional signs and symptoms.		Mistakes in admission diagnoses.		Laboratory examinations.		Location of skin lesion.	
<i>Group A.</i>											
Chest pain	7	Friction rub	3	Nausea	2	Bronchitis	3	Chest plates taken	4	T-4	1
		Râles	2			Pleurisy	3	Positive pulmon. consolidation	3	T-5	1
						Bronchopneumonia	1	Negative	3	T-6	2
										T-7	2
										T-8	2
										T-9	1
										T-10	1
										T-11	1
										On chest	2
<i>Group B.</i>											
Precordial pain	4	Dyspnea	2	Nausea	1	Cardiac failure	1	Chest plate neg.	1	T-1	1
		Dropped beats	1			Angina pectoris	2	Heart plate neg.	1	T-2	1
		Extrasystoles	1			Coronary disease	1	ECG negative	1	T-3	1
		Palpitation	1							T-4	3
		Anorexia	1							T-5	3
										T-6	1
										T-7	1
										Neck, shoulder, arm	1
<i>Group C.</i>											
Abdominal pain	25	Generalized	11	Anorexia	11	Ca. of colon	2	Colon plate neg.	1	T-4	1
		Rt. upper quad.	7	Nausea	7	Peptic ulcer	2	G.I. series neg.	6	T-5	1
		Rt. lower quad.	2	Vomiting	6	Ca. of stomach	2	G.B. series neg.	3	T-8	4
		Lt. upper quad.	2	Constipation	4	Acute and chronic chole.	4			T-9	8
		Epigastrium	3	Diarrhea	2	Acute surg. abd.	1			T-10	5
		General rebound	1	Marked distension	1	T.B. peritonitis	1			T-11	6
						Colitis	3			T-12	4
						Cirrhosis of liver	1			About umbilicus	1
						Spinal cord tumor	1			Abdomen	2
						Lead poisoning	1			Lower rt. chest	3
<i>Group D.</i>											
Lumbar pain	6	Lumbar c.v. tend.	6	Nausea	1	Pyelonephritis	2	Pyelograms neg.	5	T-10	1
		Dysuria	4	Vomiting	1	Renal colic	4			T-11	2
		Frequency	3			Hypernephroma	1			T-12	3
		Hematuria	2							Lumbar-1	3
										Lumbar-2	2
										Lumbar-4	1
										Lumbar region	1

masked the underlying disorder that errors in admission diagnoses were made. These are summarized in Table 2. It will be noted that they can be subdivided into four groups presenting (a) pulmonary, (b) cardiac, (c) abdominal, and (d) renal symptoms. In addition to this grouping there was 1 case diagnosed as lead poisoning and 1 as a spinal cord tumor. The average length of time between the onset of pain and the appearance of the rash in the visceral group was 5.5 days.

A. Pulmonary: Table 2 is self-explanatory for this group. The presence of friction rubs, râles and fever aided in obscuring the diagnosis. In only 1 of these cases could the diagnosis of a definite parenchymal pulmonary lesion (bronchopneumonia) be substantiated.

CASE 3.—An illustration is that of a 45-year-old male whose complaints were pain of 4 weeks' duration on the right side of the chest increasing with inspiration, anorexia and constipation. A friction rub was noted in the right axilla. The diagnosis of fibrinous pleurisy was made. However, on the day following admission, hyperesthesia and vesiculation were found over the distribution of the 10th thoracic nerve on the right chest posteriorly. Roentgen ray of the chest was negative and the patient was discharged as recovered in 12 days.

B. Cardiac. The common symptoms of precordial pain, often radiating down the left arm (2 cases), dyspnea, and alterations in cardiac rhythm (2 cases) led to the assumption that these patients were suffering from anginal seizures and cardiac abnormalities. In only 1 instance was a roentgenogram of the heart taken and in only 1 other an electrocardiogram, both of which were negative. Although these are the only laboratory proofs that can be offered to rule out organic heart disease, the appearance of the typical rash together with the rapid subsidence of the signs and symptoms point to the correct diagnosis of herpes zoster.

CASE 4.—A case illustration is that of a 48-year-old female who complained of severe precordial pain radiating down the left arm, weakness and nausea of 3 days' duration. An admission diagnosis of angina pectoris was made. Skin hyperesthesia was noted over the precordium. The electrocardiogram was normal. On the second day of hospitalization a typical herpetiform rash appeared along the paths of the 3d, 4th and 5th thoracic segments. The patient's convalescence was uneventful and she was discharged in 4 days.

C. Abdominal. These cases presented a variegated picture. In several instances diagnoses were made which, if not corrected, could have lead to surgical intervention and in 2 instances did. It is easily understood that when symptoms such as nausea, vomiting and abdominal pain accompanied by signs of abdominal tenderness, rigidity and hyperesthesia, present themselves to the examiner, it is only by exercising the most conservative type of diagnosis and therapy that time is allowed for the skin eruption to appear and the true nature of the disease to manifest itself.

CASE 5.—An example is that of a 45-year-old female complaining of severe pain in the right chest and right upper abdomen for 6 days, together with a rash of 2 days' duration along the path of the right 9th intercostal nerve. Cholecystographic studies were made and found to be negative. After a few days she was discharged as improved. Five months later, due to the persistence of the right upper quadrant pain, the patient was readmitted to a surgical service. At this time, tenderness and rigidity in the right upper quadrant were present. A cholecystectomy was performed on this second admission. The histologic report on the gall bladder specimen was "no pathology" (sic).

On reviewing this case it would seem that a post-herpetic neuralgia along the course of the 9th nerve should have been seriously considered prior to operation.

D. *Renal*. Those cases with pain in the lumbar region were the most difficult to diagnose. The simulation of renal disease was so marked in 5 of our 6 cases that cystoscopy and retrograde pyelography were performed with negative findings in all.

CASE 6.—An illustrative case is that of a 60-year-old female with a history of severe pain for 11 days in the right lower quadrant and right costovertebral region, accompanied by nausea, anorexia and severe headache. Two days prior to admission she developed frequency and dysuria. The pain was of sufficient severity to warrant the administration of morphine. Examination showed such rigidity and tenderness in the right abdomen and right costovertebral angle that diagnoses of postoperative adhesions, nephrolithiasis and pyelonephritis were made. However, cystoscopy and pyelography were negative. On the third day of hospitalization the typical lesions of herpes zoster appeared at the level of the 9th, 10th and 11th thoracic segments. Two years previously she had experienced a similar attack at which time appendectomy had been performed.

CASE 7 (not included in the series) exemplifies a problem of differential surgical diagnosis in the abdomen. It is the only case taken from the children's surgical service. A male child of 6 years was admitted with a history of varicella of 2 weeks' duration and right lower quadrant pain, with persistent vomiting for 5 days prior to admission. The temperature on admission was 100.8°F. There were numerous scattered varicella-like lesions over the trunk together with a deep reddish macular rash from the right costal margin to the right lower quadrant, ending abruptly at the mid-line. There was marked tenderness and moderate rigidity. No rebound tenderness was elicited. The skin seemed definitely tender and hyperesthetic. Rectal examination showed equal tenderness on both sides. There was a leukocytosis of 21,400 cells, with 66% polys., 28% lymphocytes and 6% transitional cells. Diagnoses of acute appendicitis, herpes zoster and varicella were made. After consultation with several surgeons, it was decided to operate and appendectomy was performed. The child's recovery was uneventful and he was discharged in 12 days. The pathologist's report read as follows: "Slight edema and injection of the serosa; fibrous submucosa. Diagnosis: Sclerosed appendix."

This case demonstrates the difficulty in diagnosis even though the herpes zoster is apparent on admission. The leukocytosis undoubtedly added to the obscurity for it was higher than any we had found in our adult series and is greater than that usually found in varicella.

Summary and Comment. It would be advisable to recapitulate various features that stand out in order to emphasize their clinical significance.

It is noteworthy in our series that pain is the most common and persistent complaint. The pain nearly always precedes the rash by several days. Its severity bears no relationship to the extent of the skin manifestations and patients with hardly discernible skin lesions may suffer severe segmental pain. In some cases, the pain was situated in an area widely separated from the later developing skin lesion. Most often it was present at the site where the lesion appeared.

The pain varies in intensity, duration and character. It may be hardly noticeable or may be severe enough to necessitate the administration of morphine. Usually it is dull although not uncommonly knifelike and stabbing. Sir William Jenner illustrated the obstinate persistence and severity of the pain with the history of a man who endured the excision of the affected skin, without anesthesia, in the hope of relief, but finding none, shot himself. This is in disagreement with the more modern observation that producing local anesthesia of the skin site of referred pain gives relief.

It is not our purpose to enter the debated question of the relationship between herpes zoster and varicella.^{2, 15, 16, 24a} It will suffice to call attention to our cases and to the fact that these are the cases in which evidences of more severe neurotropic and dermatropic activity were manifest. They show spinal fluid changes, motor neuron involvement, encephalomyelitis and gangrenous herpetic lesions. This might be correlated with the observations of Levaditi, Nicolau and Poincloux,¹⁷ and Zurukzoglu³¹ that the neurotropic virulence of *herpes simplex* virus and the vaccine virus is greatly increased by a previous or simultaneous inoculation with another virus.

Post-herpetic neuralgia and various paralyses have been described often, most fully by Weber,²⁹ Masten,²¹ Petren,²² Doucet and others.^{9, 13a,b, 26} Direct herniation of the lower abdominal wall has been repeatedly shown to result from various motor nerve injuries.^{6, 14, 28} Permanent injury due to the virus of herpes zoster has been proven.¹¹ It should therefore be considered as an etiologic factor in cases of direct abdominal herniation.

A mistaken diagnosis of erysipelas can be made in those cases in which the marked erythematous area about the herpetic vesicle attains a fiery red appearance and extensive spread. It has been reported^{4, 23, 24b} that the appearance in these cases is due to secondary infection. In those of our cases which were mistakenly diagnosed as erysipelas, secondary infection did not appear to be a factor.

The simulation of visceral disease by herpes zoster has been noted in isolated instances. Cabot⁵ has called attention to herpes zoster in the differential diagnosis of lumbar pain. Both Osler¹⁹ and Strumpell²⁵ mention the simulation of thoracic zona to pleurisy. Curtin⁷ reported 10 cases with involvement of the serous membranes,

pleuritis and peritonitis. Litchfield¹⁸ presented a case simulating renal colic and a second simulating cholelithiasis. He quotes Marinacci²⁰ who described a case misdiagnosed as generalized peritonitis. Blanton³ noted the similarity to nephrolithiasis in 1 case and Barney¹ reported a case in a man already operated upon for gall bladder disease. Young³⁰ presented 4 cases 1, which resembled acute appendicitis and 3 which simulated renal disease. Davis⁸ has suggested the interesting hypothesis of post-infectious inflammation of the posterior root ganglia in children, associated with the common cold. The title of his paper "Segmental Neuralgia in Childhood Simulating Visceral Disease" is self-explanatory. He believes that relationship to true herpes zoster is quite plausible. It has been shown at autopsy that the posterior ganglia can be pathologically involved by the virus of herpes zoster without causing a demonstrable skin lesion.¹⁹ Hence it is conceivable that the predominance of a factor in the zona virus, corresponding to the encephalogenic (neurotropic) factor of the virus of *herpes simplex* may produce pain without the characteristic skin lesion, this latter being a function of a keratogenic (dermatropic) factor present in the virus.

Head¹² first observed that herpes zoster affects most frequently those ganglia which receive sympathetic fibers. The herpes zoster virus may travel both (centrifugally) toward the skin and (centripetally) toward a viscus²⁷. Instances of symptoms indicative of pleural or peritoneal irritation have been noted.^{1, 7, 10, 18, 20, 30} One must attempt to explain the recognizable clinical signs of actual organic involvement such as friction rubs and the like. It is, of course, probable that a concomitant involvement of an organ by an unrelated process may give rise to these signs, but one must also consider that a virus infection of the organ itself may occur due to direct transmission along vegetative pathways by virtue of the bi-directional nature of the virus.

In the differentiation from intrathoracic and intraabdominal lesions, there are several points which are noteworthy. The radicular nature of the pain, the hyperesthetic zone, stopping at the mid-line, the superficial nature and radiation of the pain toward the back, are points of differential diagnosis even in the absence of the characteristic skin rash. Careful examination of the back will sometimes reveal a single vesicle which is the herald of a future lesion. The normal leukocyte count is a constant finding in uncomplicated herpes zoster. The more difficult differential diagnosis seems to be from renal colic in which even hematuria may be present to accent the simulation. In all these instances, knowledge of the above mentioned symptomatology, a careful physical examination and recourse to the usual diagnostic procedures will be necessary before the true nature of the malady can be disclosed. Aid in diagnosis and therapy may be attained by injection of the involved nerve or nerves with 2% novocaine.

In conclusion, it should be emphasized that herpes zoster in the early stages before the appearance of the typical rash may so closely simulate a visceral disease both in symptomatology and findings that a differential diagnosis may be extremely difficult. This association must be much more common than is usually recognized for communication with many practitioners has revealed isolated instances in individual experience. It must be borne in mind constantly to prevent unfortunate diagnostic and therapeutic mistakes.

We acknowledge our obligation and appreciation to Dr. Charles Nammack for permission to use cases from his medical service and for his intercession in obtaining consent to use cases from the other medical services, and to Dr. Carl Burdick for the use of the surgical material presented in this article.

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TRUE HERMAPHRODITISM.

REPORT OF CONFIRMED CASE.

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TRUE hermaphroditism is a term correctly applied only to individuals with both male and female gonads. The glands may be discrete or fused to form an ovotestis. Truly, however, the term

demands functioning glands and accessory organs of both sexes in the same person.

Several types of true hermaphroditism have been described and an elaborate scheme covering the possible forms was devised by Klebs-Sauerbeck, but as Young³ points out this classification is too complex for practical use. He regards the following nomenclature of the different varieties as now generally accepted:

(a) Lateral true hermaphroditism: An ovary on one side and a testicle on the other.

(b) Unilateral: Both ovary and testis on one side and one gonad on the other.

(c) Bilateral: Both ovary and testis on each side.

Young³ has carefully reviewed the literature of hermaphroditism in general and accepts 20 cases of true hermaphroditism including 1 of his own. All of these cases have been proven microscopically. Other cases which are probably true hermaphroditism have been reported by a number of authors, but unless both ovarian and testicular tissue was demonstrated microscopically it was not accepted.

In an analysis of the proven cases Young³ found that the bisexual condition was discovered by herniotomy in 7 cases, by laparotomy in 6 and by autopsy in 7. All but 4 patients had passed the age of puberty, and 12 were beyond the age of 20 before the condition was discovered. The libido of the individual patient corresponded to the manner in which he had been reared in all but 1 case in which no note was made. (In our case, the emotional drive was the opposite of that of the manner in which he had been brought up.) Six patients living as males had menstruated—in 5 through the urethra. One had periodical nose bleed and abdominal pain. Four of these had coitus with women, none with men. Young's own case had never menstruated although apparently normal ovulation had gone on for years. Two cases with lateral hermaphroditism began to menstruate through the urethra at the age of 15. There is no record of a patient practicing bisexual coitus. In 4 adult cases reared as females only 1 had coitus as a female and this occurred after a testis in the scrotum had been removed. A penis-like phallus was present in each case but there was hypospadias in all but one. In Young's case, an operation was performed to create a penile urethra.

Our case bears interest not only from the anatomical standpoint but because of its important medico-legal and psycho-sexual aspects.

Case Report. Eloise H., a 27 year-old negro (who for the sake of convenience we shall speak of as "he" although the pronouns "he", "she" or "it" are probably equally suitable) came to the attention of the civil authorities in January, 1935. At that time he was living with a woman who had deserted her husband and her 3 children. His mistress was pregnant but claimed that her husband was the father of the coming child. However, the husband denied the paternity of the child and the patient was accused of being the father. In April, 1935, this woman was delivered of a male infant.

In view of the part the patient had played in disrupting the marital union, in addition to the suggestion of his hermaphroditic nature and possible paternity of the new born child, he was brought before the Municipal Court on a bench warrant. Two court physicians examined him, made a diagnosis of "pseudo-hermaphroditism and inguino-scrotal hernia" and estimated his mental status as being that of a "low grade moron with very poor comprehension and childish reasoning." Later observation indicated that although a moron he was above the low grade level and had a fair degree of social adaptability.

On January 15, 1936 he was committed to the Philadelphia General Hospital, Psychopathic Ward, for observation. On admission, the patient was fully attired in female clothes from hat to chemise but was placed in the men's division because of what seemed to be a predominantly male type of pseudo-hermaphroditism.

In relating his history Eloise was quite coöperative and frank in all details but spoke a bit coyly in reference to sexual matters. He stated that at the time of his birth in a small southern town there was a dispute between two attending physicians as to his sex. It was then decided that the site whence the urine came would determine whether he was to be brought up as a male or female and in view of the hypospadias it was decided that he should be considered a girl. At that time one of the physicians suggested amputation of what was thought to be a redundant clitoris. This was objected to by the family and the operation was not performed. Hence the child was looked upon as a girl and was clothed in dresses throughout his life. He was regarded by his family much more as a female than as a male, although they were cognizant of the fact that he was somewhat "half and half".

He described erections beginning about the age of 12 and claimed to have had "ejaculations" when 14. He related numerous episodes in his youth wherein he was involved in various sexual activities with females. His associates were usually males who recognized his unusual sexual status. He has had numerous female friends with whom he has engaged in regular sex relations as a male and as far as we know has never manifested sexual interest in men. Ejaculations, however, are said to be scant in quantity and emanate from the orifice below the erectile organ. As previously mentioned, he had become involved with a married woman who had taken such a fancy to him that she neglected her husband and finally separated from him. This woman became pregnant and was delivered of a child, the paternity of which was questioned. The patient claimed that there were two reasons why he was not the father of this child. First, that the woman was one month pregnant when he first met her and second that there was no intra-vaginal insemination. His work has been of the domestic type and for some time had a regular job in this capacity in a private family where he was considered without question a female.

He denied all menstrual phenomena. He stated that there had never been any turgescence of the breast, no periodic malaise, colicky pains or bloody discharge. He had always thought himself sexually a male, but anatomically somewhat "half and half."

The patient's sister told a different story but it is difficult to say whether she may not have been somewhat prejudiced in the matter, inasmuch as she had always considered Eloise a female sibling. She stated that she had noticed for a period of several years, during which the patient lived with her, various menstrual phenomena which convinced her that the patient was a female. She had found on several occasions that Eloise's underclothes were blood stained and noticed that his breasts became full at monthly intervals. At such times Eloise would sit around apparently with malaise and complained of colicky pains.

Physical Examination (Figs. 1 and 2). The patient is a fairly well nourished, young colored individual, who appeared not at all disturbed by the examination and was quite coöperative. General body build, facial configuration and voice are suggestive of a female type. The face has a scant beard growth on the sides and practically none on the chin and adjacent areas. The skin is fine and velvety in texture and the legs have a female contour. The fingers are unlike a male negro's but are quite long and slender. There are some scattered tufts of hair on the anterior chest. The pubic hair has more of a female distribution, tending to be delineated by a horizontal pubic line although there is a small amount of

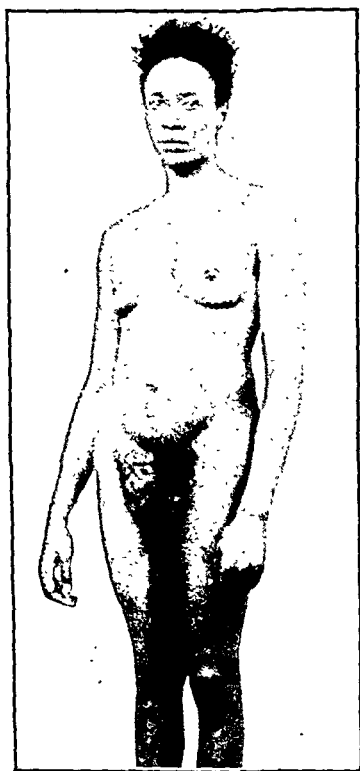


FIG. 1



FIG. 2

FIG. 1.—Picture taken prior to operation showing female contour and large right inguinal hernia and phallus.

FIG. 2.—Lateral view prior to operation.

hair extending toward the umbilicus and on to the inner surfaces of the thigh. The chest is well developed, breasts being quite large, the size of small cantaloupes and contain abundant glandular tissue. There are well demarcated areolae and well formed nipples. To all intents and purposes these may be said to be perfect female breasts. There is some protuberance of the abdomen in the lower portion. A rather prominent mons veneris is present. A modified perineal hypospadias exists and the scrotum is cleft so as to resemble the labia majora (Fig. 3). In the right labium there is a hernial sac containing bowel. The right inguinal ring admits two fingers and the content of the sac is reducible. A small lump of the consistency and sensitivity of a testicle, is found in the right labium but moves with

the contents of the sac on reduction. No epididymis is palpable but a firm, cord-like structure is felt in the inguinal canal. No testicle or cord is palpable on the left. The urethral orifice is located posteriorly just in front of the anus between lateral diminutive labia minora. The erectile



FIG. 3.—View showing scrotal-like sac with hernia reduced, and phallus.

organ (Fig. 4) is about $2\frac{1}{2}$ inches long and has a prepuce. It would appear that the presence of the undeveloped labia establishes the space bounded within them as a vestibule and in this respect differs from a simple hypospadias of the perineal type. A rectal examination revealed two small prostatic lobes, the right being larger and more definite than the left. A



FIG. 4.—View showing primitive labial folds and urethral orifice.

cervix cannot be palpated. The spine has an exaggerated lumbar lordosis making for greater lower abdominal protuberance.

Laboratory Studies. Female sex hormone studies showed "no anterior pituitary hormone and high-normal intermenstrual phase female sex hormone

content." Male hormone study by the cock's comb method done by Dr. L. P. Hansen and Dr. J. F. McCahey revealed a quantity comparing with a low-normal for a male. Dr. H. W. Ostrum, reporting on the skull roentgen ray stated: "The bones of the skull are normal. The sella turcica is well outlined and is normal in size. The dorsum and clinoid processes show no evidence of involvement and the pineal body is normally situated."

On February 1, 1936, Dr. E. L. Eliason did a classical right inguinal herniorrhaphy and explored the pelvis through the large internal ring. Upon opening the hernial sac an organ was found lying close to the internal abdominal ring, attached to a broad pedicle of peritoneum, coinciding with the mass thought to be testicle by external palpation. It measured 2.5 by 1.5 cm. and was somewhat ovoid in shape, presenting an external appearance not unlike an ovary with an irregular surface which suggested areas of old follicular rupture. However, when a small incision was made, the bulging, cut surface had the appearance of testicular substance. A quick section report was obtained at the time of operation and a paraffin section made subsequently. The broad pedicle of peritoneum was traced across to the opposite side of the pelvis, but no corresponding organ was palpated. There was no evidence of epididymis or corresponding embryonic structure as is at times found in the female. At the upper border of the broad ligament (the term which we apply to the peritoneal folds) was a definite tubular structure with a fimbriated end. Running near the other border was a firm cord-like structure extending down the inguinal canal. This was obviously a round ligament. Embedded in the broad ligament, medially, at what seemed to be the junction of the Fallopian tube and round ligament, was a bulbous structure measuring approximately 4 by 3 by 2 cm. This was brought to view with difficulty and the presence of an associated channel down through the perineum could not be ascertained (this, of course, was due to the limited opening permitted by the internal ring). There was a fine white linear structure running transversely across the broad ligament which corresponded probably to a vas deferens or duct of Gartner. Examination for seminal vesicles and prostate was not done. The operation was terminated by placing the glandular structure in abdomen and completing the herniorrhaphy.

Microscopic examination of the biopsy specimen (Dr. R. P. Custer): "The small fragment was examined by the Ultropak method during operation. A tubular pattern was noted and the specimen reported as 'probably testis.' Paraffin section shows it to present two clearly demarcated portions (Fig. 5), the first of which exhibits a loose fibrillar background containing small, round and spindle cells and clumps of larger cells with acidophilic cytoplasm resembling testicular interstitial cells; irregularly distributed are tubulo-glandular structures (Fig. 6) some of which are solidly filled with hyperchromatic epithelium, others showing imperfect lumina and presenting atypical spermatogenesis; no clearly defined adult spermatozoa are identified, however. The other segment (Fig. 7) shows typical, compact, spindle celled ovarian stroma containing a few germinal follicles." Diagnosis: Ovo-testis.

Eloise made an uneventful recovery from the operation. He mingled freely with the male patients and helped considerably about the ward. He wished to be treated as a man and do a man's work rather than housework. He was quite appreciative for the hernia repair and for being regarded as a man, feeling sure that he would never again put on female clothes. When questioned about sexual desires 2 weeks after the operation, Eloise said that he would like to be with a woman and was missing his sex relations but did not seem at all worried about his unusual sexual status. The name "Louis," which he assumed, agreed with his ego more than "Eloise."



FIG. 5.—*Ovo-testis*. Low-power view showing testicular segment on left, ovarian on right, with sharp line of demarcation but no intervening septum. (Mag. 69 \times .)

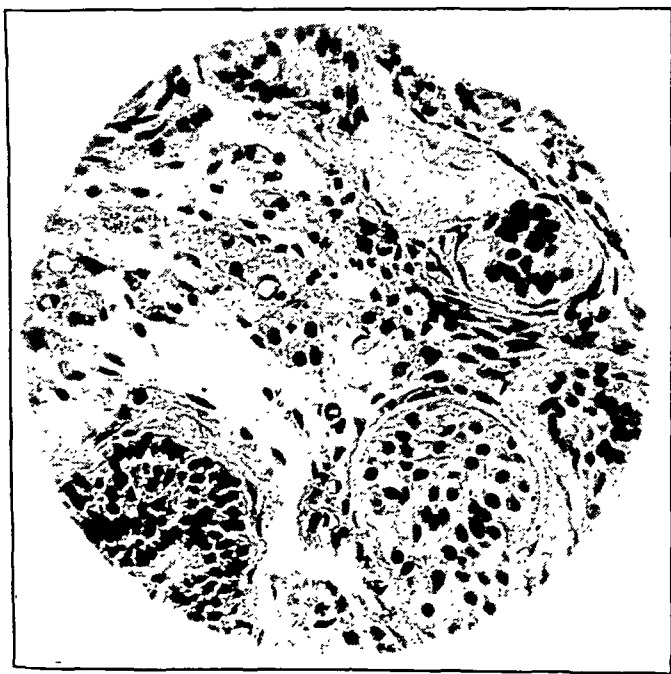


FIG. 6.—*Testicular segment*. Showing interstitial cells (center) and immature spermatogenic tubules. (Mag. 368 \times .)

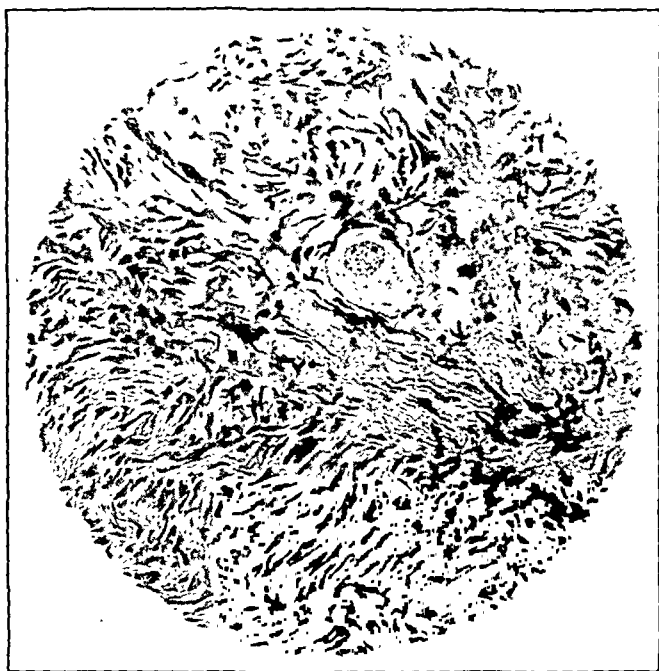


FIG. 7.—*Ovarian Segment.* Illustrating characteristic stroma and primary germinal follicle with ovum

From a psychological standpoint the case offers interesting material for speculation. We must consider the possibility of this individual being psychologically a homosexual female; but by making the patient male, the perversion socially ceases to exist. This, of course, is desirable from the standpoint of the community.

We know that anatomically he is bisexual and the evidence would seem to indicate that the male and female sex drives are very nearly equal. Therefore, the patient should be capable of psychologically turning either way. The direction in which such a person is likely to swing must depend to a great extent on environmental and physical factors.

Endocrine factors in such a case may not be the dominant force in determining the sex. Here we have to consider the importance of organ predominance or, let us say, the opposite organ inferiority as having considerable bearing on the direction taken by the sex activity. This would be borne out by the cases reported by Novak¹ in which the amputation of a hypertrophied clitoris caused the patients to show an increased femininity. However, had we looked upon our patient as being predominantly feminine and accordingly amputated the organ which can be considered either a penis or a hypertrophied clitoris, he would have been left practically sexless since the female side of the external genitalia was not developed. It seemed wisest to convert him into a male. In an individual with external female characteristics a psychic swing toward the masculine is termed gynandrisms; conversely, a swing toward a feminine personality in a male is termed androgynism. Washburn² states that androgynoids are said to indulge in spontaneous phantasy and delusions from which they derive much pleasure. It is characteristic of these individuals to desire to dress in the clothing of the opposite sex (transvestitism). Since our patient has been wearing men's clothing he has exhibited no overt desire to return to the female method of dress. This would be evidence against the belief that he may be psychologically a homosexual female.

Summary. We report a 27-year-old negro individual who has been bisexual anatomically, as far as one can logically conceive bisexuality, ever since birth. In retrospect, the suggested amputation of the phallus at birth would probably have been disastrous to the patient because of his subsequent male tendencies, psychologically at least, and possibly endocrinologically. The predominantly male type of phallus probably influenced his masculine trend considerably as far, at least, as lending itself to sex relations. How far the endocrine drive entered the situation is difficult to evaluate since we are unable as yet to say whether the patient is predominantly male or female from a hormonal standpoint.

Conclusions. Following Young,³ our case is analyzed in the accompanying table.

<i>Source of material.</i>	<i>Age.</i>	<i>Reared as.</i>	<i>Emotions.</i>	<i>Bodily aspects.</i>	<i>Menses at ? age.</i>
Right herniotomy, gonadal biopsy	27	Female	Male	Female	Late adolescence (?)
<i>Phallus hypospadiac ?</i>	<i>Vaginal opening ?</i>	<i>Uterus located ?</i>		<i>Right gonad.</i>	<i>Left gonad.</i>
Penis-like hypospadiac	Into urethra (?)	Uterus in pelvis		Ovotestis in hernia	Not seen

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EVIDENCE OF COMMUNICATION BETWEEN RENAL AND OMENTAL BLOOD VESSELS FOLLOWING NEPHRO- OMENTOPEXY FOR ARTERIAL HYPERTENSION IN MAN: PRELIMINARY NOTE.

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THE classic work of Goldblatt and his associates¹ on the production of hypertension in dogs and monkeys by constricting the main renal arteries stimulated the present investigation. These workers noted that in animals with experimental hypertension, whenever the blood pressure fell to a lower level it was due either to inadequate clamping of the renal arteries or to the development of an adequate collateral circulation by the kidney (ureteral and capsular vessels). This observation led Goldblatt² to state (May 19, 1938) that an obvious surgical procedure in the treatment of hypertension in man which suggested itself from this work was the possible improvement of the vascular supply to the kidney by increasing the accessory circulation.

Since August, 1937, we have undertaken in 8 patients with hypertension, an operative procedure designed to improve the renal circulation (right kidney only) by providing it with an accessory circu-



FIG. 1.—Omentum adherent to kidney 2½ months after nephro-omentopexy. Note the relatively large caliber of the omental vessels and India ink in the renal capillaries and arterioles. (Hematoxylin and eosin, $\times 78$.)



FIG. 2.—The omentum 4 cm. from the kidney. Note India ink in the omental vessels which was originally injected into the renal artery. (Hematoxylin and eosin, $\times 68$.)

lation (omentum). This was accomplished by approaching the kidney through the abdominal route, decapsulating the organ and enveloping it in a new fatty capsule of omentum. The details of this procedure will be described elsewhere.

Of utmost importance was the question whether the omentum would provide a collateral blood supply to the kidney. This was answered by the following observation: a male, aged 38, with a history of hypertension (essential type) of 4 years' duration (referred by Dr. David S. Likely), died from a massive intra-abdominal hemorrhage due to necrosis and rupture of the main branches of the coeliac axis artery 2½ months after right nephro-omentopexy was performed. At necropsy (Dr. S. Milton Rabson), the right kidney with its adherent omentum and contiguous organs were removed en masse. The right kidney was perfused by means of a hydraulic system in which air pressure was obtained by water displacement. A carboy in the circuit containing physiologic saline was connected by rubber tubing and cannula to the renal artery. A manometer attached to the unit gave an accurate index of the intra-arterial (renal) pressure. This was maintained between 180 and 200 mm. of mercury (somewhat lower than the brachial artery pressure noted during life). After perfusion with saline, a suspension of India ink in water was injected into the tube leading to the right renal artery and the kidney perfused with the India ink-saline suspension. This was followed by perfusion-fixation with Helly's solution.*

On gross examination, it was noted that the lower pole of the anterior surface of the kidney which was not completely covered by omentum first assumed the color of the ink, but immediately thereafter, the India ink was seen to spread out into the omentum beyond its attachment to the kidney. Figure 1 is a photomicrograph demonstrating the adherence of the vascular omentum to the kidney. Figure 2 shows India ink which was injected into the renal artery in the ommental vessels 4 cm. from the kidney.

Our results, in terms of the effect of this operation on blood pressure, have been encouraging and it is hoped that the bilateral nephro-omentopexies now planned will be more effective. This report is made solely to indicate that communication between renal and ommental blood vessels can be established by nephro-omentopexy in man and that such a procedure may supply effective accessory circulation to the human kidney.

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* Nine parts Zenker's solution and 1 part 100% formalin.

PULMONARY AND URINARY EXCRETION OF PARALDEHYDE IN DOGS.

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A BETTER understanding of the fate and elimination of paraldehyde by the body is especially desirable at the present time because of the recent increase in the therapeutic use of this drug, particularly in the field of obstetrics,^{1,5,7,10,11} and since such information as has been reported in the literature is peculiarly scarce, incomplete, and of a contradictory nature. Uncertainty exists in regard to the routes and duration of excretion as well as to the actual amounts eliminated, and there is apparently no evidence as to what disposition is made of the vastly larger amount which is not excreted by the body.

In 1899 Raimann⁹ reported that of 50 gm. of paraldehyde administered to each of 2 patients, the largest amount eliminated was excreted unchanged by the lungs, a smaller amount by the skin, and a very small amount by the kidneys, and suggested the possibility that a larger portion is burned in the body than is excreted. Wood¹² asserted that paraldehyde escapes from the body unchanged in part through the lungs and in part through the kidneys, the elimination being rapid, but enough remaining in the system to give an odor to the breath for many hours. Cushny² maintained that the drug is excreted in part by the lungs, but mainly by the urine. La Rue⁶ administered paraldehyde by stomach to dogs in doses of 1.8 gm. per kilo, and found that its concentration in the blood was greatest about the fourth hour, and that it had entirely disappeared from the blood by the twenty-fourth hour. There was a trace remaining in the urine at this time, but none at the end of the thirty-first hour. He concluded that the drug was entirely oxidized in less than 15 hours, and that doses of less than 2 gm. were not fatal to dogs. Unfortunately, each statement is based on the results of one experiment only. Recently Nitzescu⁸ and his co-workers reported results on the analyses of tissues and excretions of rabbits and dogs following the intravenous administration of paraldehyde in doses of 0.2 gm. per kilo. They found the drug in the amounts of 8.8 mg. per 100 cc. of urine, and 28 mg. per 100 gm. of expired air. In further experiments on rabbits and rats injected intravenously with 1 gm. per kilo of the drug, these investigators found that the rabbits eliminated 22.8% by the lungs in 10 hours, while the rats excreted the entire amount by this route in the same length of time.

Since we felt that the confusion appearing in some of these reports was based to some extent on conjecture, limited experimental work and perhaps faulty analytical methods, we decided to investigate the comparative elimination of paraldehyde by the lungs and kidney in dogs which had received the rather large, full anesthetic dose of 1.8 cc. per kilo by rectal administration.

Experimental Procedure. The experimental animals used were 3 female dogs weighing from 5.8 to 9.8 kilo. Usually food was removed from the animals overnight, but water was allowed *ad libitum*. After the rectum had been thoroughly washed out with warm water, paraldehyde was slowly administered by this route in the dosage of 1.8 gm. per kilo, mixed with 1.5 to 2 cc. of benzyl alcohol, the animal being held quietly in a prone position until complete anesthesia occurred in 40 to 90 minutes. No animal was used oftener than once in 2 weeks. One preparation only of Eastman's No. 198 paraldehyde, aldehyde-free, was used in these experiments, after it had been found by actual tests to meet the requirements of the United States Pharmacopœia, 11th edition.

Normally, 10-minute samples of the expired air were collected hourly over periods averaging 7 hours in length. Occasionally the collection periods were longer, and in some experiments the observations were continued over more extended periods of time, to determine approximately when the drug had disappeared from the expired air (and urine).

The urine was collected by catheterization, the bladder being emptied at the end of each hour. Before the experiment began the animals were encouraged to drink water, so that there would be sufficient amounts of urine for the analyses, and in the last test (Table 2) a large amount of physiologic saline was injected intravenously to determine its effect on the excretion of paraldehyde.

Methods. Since paraldehyde is comparatively inert chemically, it must first be converted into acetaldehyde for its quantitative determination in small amounts. After considering various methods for the determination of acetaldehyde, one employing the principles of Nitzescu, Georgescu and Timus⁸ was selected, as it alone offered the possibility of determining paraldehyde as acetaldehyde in the large amounts of air respired by dogs, and was completely satisfactory for determinations of the same substance in urine. The principles of this method consist of drawing paraldehyde-laden vapors from air or urine through hot 10% sulphuric acid, thus forming acetaldehyde by depolymerization. The acetaldehyde-water vapor mixture then passes through a condenser into a twentieth-normal solution of sodium bisulphite, with which the aldehyde forms an addition compound. The excess bisulphite is then neutralized with twentieth-normal iodine solution, an excess of saturated sodium bicarbonate solution is added, and the liberated bisulphite is titrated with two hundredth-normal iodine solution, 1 cc. of which is equivalent to 0.11 mg. of paraldehyde.

Because of the large amounts of air involved, it was found necessary to substantially augment and modify the apparatus as well as the method outlined above. A specially constructed mask with inlet and outlet valves was devised which fitted snugly over the muzzle of the dog, and through

which air was sucked continuously, passing into one end of a rubber anesthesia bag which served as a reservoir for excess air expired at a faster rate than could be taken care of by the suction. From the distal opening of the anesthesia bag the air passed into and through four 30 mm. glass tubes 28 cm. in length, each of which contained about 75 cc. of 10% sulphuric acid forming a column 12 cm. in depth. These tubes, which were widened to 40 mm. in diameter immediately above the surface of the acid to prevent loss of acid through excessive bubbling, were connected in series and suspended in boiling water. The acetaldehyde-laden vapors were drawn from the last tube through a water condenser into a cylinder containing about

TABLE 1.—EXCRETION OF PARALDEHYDE BY THE LUNGS.

Dog No.	Amount of paraldehyde administered, gm.	Hours after adminis- tration.	Length of air collection period, min.	Paraldehyde recovered in collection period, mg.	Amount of paraldehyde estimated for each hour, mg.	Estimated paraldehyde excretion for 7 hours.	
						Gm.	%
4	10.4	1	13	11.1	28.1	0.387	3.7
		2	14	14.3	56.2		
		3	30	12.5	34.5		
		4	30	24.4	37.8		
		5	30	37.3	61.7		
		6	30	45.6	82.5		
		7	30	42.3	86.4		
		24	25	17.5			
48	10	0					
6	17.6	1	10	6.0	20.1	0.523	3.0
		2	15	12.0	42.8		
		3	10	16.2	75.5		
		4	10	15.5	94.1		
		5	10	15.2	93.0		
		6	10	15.3	93.0		
		7	10	19.3	104.0		
		11	10	19.3			
		14	10	15.9			
		24	10	1.3			
		30	10	1.1			
5	13.7	1	10	4.5	15.9	0.413	3.02
		2	10	7.9	39.5		
		3	10	16.2	75.8		
		4	10	14.3	90.5		
		5	10	12.4	78.5		
		6	10	7.4	57.9		
		7	10	10.5	55.0		
		24	10	0.9			
30	10	0.9					
5	16.7	1	12	4.4	12.2	0.445	2.7
		2	10	7.7	35.3		
		3	10	11.6	59.0		
		4	10	15.1	80.5		
		5	10	16.8	97.0		
		6	10	14.6	93.0		
		7	10	9.1	68.0		
		24	10	1.1			
		30	10	1.1			
		54	10	0			
4	10.8	1	10	2.8	9.9	0.280	2.6
		2	10	4.7	23.0		
		3	10	6.3	32.9		
		4	10	8.0	43.2		
		5	12	13.4	59.1		
		6	10	7.7	56.0		
		7	10	10.5	56.0		
5	16.0	1	10	1.4	3.9	0.311	1.9
		2	10	5.2	20.2		
		3	10	5.0	30.0		
		4	11	14.0	61.0		
		5	10	11.0	72.4		
		6	10	9.1	57.3		
		7	10	11.8	62.7		
						2.8	
Average							

400 cc. of a twentieth-normal sodium bisulphite solution forming a column of liquid 24 cm. in height, which completely removed the acetaldehyde. The contents of this cylinder were diluted to 500 cc. with distilled water after all the air-vapor mixture had been drawn through it, and 10 cc. samples were titrated as described above, using the formula: cc. N/200 iodine $\times \frac{500}{10} \times 0.11 =$ mg. of paraldehyde.

When the paraldehyde content of urine was being determined, a measured amount of urine was placed directly in the first tube of hot sulphuric acid, and a stream of air sucked through the apparatus in exactly the same manner as described above, for one-half hour. The formula for calculating the urine paraldehyde was as follows:

$$\frac{\text{total cc. of urine}}{\text{cc. of urine used}} \times \frac{500}{10} \times \text{cc. N/200 iodine} \times 0.11 = \text{mg. of paraldehyde.}$$

Since acetone will also form an addition compound with sodium bisulphite, each sample of urine was tested for this substance by the sodium nitroprusside reaction of Rothera.⁴ All such tests were negative.

Before the above described method for aldehyde determination was used in the experiments on animals, numerous tests were made to determine its value and limitations, using accurately weighed amounts of paraldehyde. When a stream of air was drawn through a flask containing pure paraldehyde, an average of 90% of the latter was recovered, and when an aqueous solution of paraldehyde was placed in the first sulphuric acid tube the recovery was complete. The loss of 10% in the first procedure is probably due to some condensation of paraldehyde in the rubber anesthesia bag, but is more than balanced by the increased respiration observed in all animals when the mask was applied, and which could not be obviated. The use of the Douglas bag for collecting large amounts of air was discontinued after several tests not herein reported, because of loss of paraldehyde probably from condensation on the inner surface of the bag, and because a very large sample of air could not be analyzed before it was time to collect the next sample. Continuous collection of air by keeping the animal in a closed chamber was not feasible because the water pump used could not draw the air rapidly enough through the apparatus, and because the probability of paraldehyde condensation on the inner surfaces of such a chamber was increased, paraldehyde having a boiling point of 124° C.

Much additional work was necessary to adjust the whole system so as to make certain that the paraldehyde was completely converted into acetaldehyde, and that all of the latter was trapped by the bisulphite solution, these results depending on the volume of air and the rate at which it could be drawn through the apparatus. The limited suction power obtainable from the water pump used usually precluded the possibility of collecting samples of air for longer than 10 minutes, since the expired air from even the smaller dogs filled the anesthesia bag reservoir during that time, despite the fact that air was constantly being drawn from it.

Results. *Excretion of Paraldehyde by the Lungs.* The actual amounts of paraldehyde recovered from the expired air of 3 dogs during the collection periods over 7 hours of observation, as well as the total amounts estimated for this time, are contained in Table 1. While it is possible that the figures for the estimated output of paraldehyde over the whole 7-hour period, calculated from the shorter collection periods, are only approximate, they nevertheless indicate that a relatively small amount of the drug, averaging 2.8%, is eliminated by the lungs over 7 hours, and how slowly it is elimi-

TABLE 2.—EXCRETION OF PARALDEHYDE BY THE KIDNEYS.

Animal No.	Amount of paraldehyde administered (gm.)	Hours following paraldehyde.													Paraldehyde excreted in 7 hours, %.
		1.	2.	3.	4.	5.	6.	7.	11.	14.	24.	30.	48.	54.	
4	10.4	Urine (cc.) Paraldehyde (mg.)	63.0 17.7	6.5 8.9	7.0 10.0	13.0 21.1	17.5 28.1	18.0 26.8	17.5 25.7	..	9.0 6.6	..	23.0 2.6	..	1.3
6	17.6	Urine (cc.) Paraldehyde (mg.)	45.0 14.8	25.0 21.1	48.0 90.6	59.0 102.2	21.5 35.0	28.5 39.1	23.0 30.5	12.0 11.5	40.0 9.8	18.0 2.5	2.0
5	13.7	Urine (cc.) Paraldehyde (mg.)	68.0 29.9	47.0 38.8	4.5 5.0	3.0 4.1	4.5 5.0	6.3 10.3	7.0 9.2	..	83.0 12.0	0.75
5	16.7	Urine (cc.) Paraldehyde (mg.)	14.0 7.7	9.5 7.3	3.5 2.9	5.5 7.1	4.5 7.4	13.5 20.1	10.5 16.2	..	62.0 13.6	56.0 12.3	..	8 0	0.4
4	10.8	Urine (cc.) Paraldehyde (mg.)	12.6 4.9	44.0 41.1	10.5 13.9	18.5 26.5	16.5 25.4	17.5 26.0	19.0 27.6	1.53
5	16.0	Urine (cc.) Paraldehyde (mg.)	15.0 6.6	75.0 49.5	43.0 40.2	5.0 5.5	7.0 9.6	34.0* 44.9	95.0† 125.4	1.76
Total	85.2	Total cc. of urine	218.0	207.0	116.5	104.0	71.5	117.8	171.5	52.0	194.0	74.0	23.0	8	1.29 Average
		Total mg. of paraldehyde	82.1	166.7	162.4	166.5	110.5	167.2	234.6	56.0	42.0	14.8	2.6	0	
		Average mg. of paraldehyde per cc. of urine	0.38	0.81	1.39	1.6	1.54	1.42	1.37	1.08	0.96	0.22	0.11	0	

* 30 cc. of physiologic saline injected intravenously in the fifth hour.

† 500 cc. of physiologic saline injected intravenously in the sixth hour.

NOTE.—In 3 experiments not reported in this table, paraldehyde had disappeared from the urine at the end of the twenty-fourth hour in 1 animal, and at the end of the forty-eighth hour in the other 2.

nated by this route. Apparently the maximum excretion of paraldehyde by the lungs occurs from the fourth to the seventh hour and diminishes markedly from the seventh to the twenty-fourth hour, being practically negligible after that time.

Excretion of Paraldehyde by the Kidneys. In contrast to the gradual increase in the elimination of paraldehyde by the lungs during the 7-hour period, excretion of the drug by the kidneys is dependent mainly on the amount of urine (Table 2). Up to the third hour there is a progressive increase in the amount of paraldehyde per cc. of urine, but from then on through the seventh hour the amount of paraldehyde per cc. of urine remains rather constant. The determinations made after 14 hours do not indicate the entire amount of drug eliminated after that time, but the marked decrease in percentage of paraldehyde per cc. of urine indicates a marked decrease in its elimination by this route. After 24 hours the amount of paraldehyde in the urine is practically negligible, as in the case of the expired air.

In the final experiment on Dog 5, 30 cc. of physiologic saline was injected intravenously during the fifth hour, and 500 cc. during the sixth hour, and the resultant increase in urinary output was accompanied by proportional increases in paraldehyde elimination, the amount per cc. of urine being entirely in agreement with the average for all animals during those hours.

Discussion. While La Rue⁶ concluded that the administration of paraldehyde to dogs by stomach in doses of 2 gm. per kilo was not a fatal dose, we found that 1.8 gm. per kilo by rectum was sometimes fatal, but autopsies yielded no positive information as to the cause of death. The complete anesthesia which invariably occurred from this dose within 40 to 90 minutes always lasted through the 7-hour period of observation and usually for several hours longer. The results of only 6 of these experiments on 3 dogs are reported in this paper, since observations on the expired air and urine for the 7-hour period were not always obtainable because of early death of the animal, loss of paraldehyde from the rectum, or other experimental accidents.

La Rue found that the highest concentration of paraldehyde in the blood occurred around the fourth hour in the one experiment which he reports. This is in agreement with our finding that the highest concentration of paraldehyde per cc. of urine occurred at this time, although this concentration was fairly uniform in the urine from the third to the seventh hour inclusive, ranging from 1.4 to 1.6 mg. per cc. Since Dog 4 died within 24 hours, after the air and kidney excretion of the drug had considerably diminished—the concentration of the drug in the urine having fallen after the fourth hour—it would seem probable that a maximum blood concentration or kidney threshold for paraldehyde occurred within the 7-hour period.

Although the mask was so constructed as to offer a minimum of resistance to respiration and to avoid rebreathing, there was always a noticeable increase in respiratory rate and amplitude following its application. Since the hourly output of paraldehyde is calculated from the amount present in the sample obtained when using the mask, it is believed that the estimated output tends to be in excess of the amount actually eliminated, since the respiratory rate and volume were lower during the balance of the hour. In the six experiments reported, the 1.3% average excretion of the drug by the urine and 2.8% average estimated for the lungs is surprisingly small over the 7-hour period; since both amounts fall off sharply after that time, the question is logically raised as to what disposal is made by the body of the far greater amount which was not eliminated in its original form. Our findings do not agree with the statement of Cushny² that most of the drug is eliminated in the urine, although our results indicate that any means used to increase the output of urine would hasten the elimination of paraldehyde by this route. While Raimann⁹ stated that an amount is excreted in the insensible perspiration which is intermediate between that eliminated by the lungs and kidneys, his belief is unsupported by experimental data, and the high boiling point—124° C.—of paraldehyde would not appear to lend support to this theory. We do, however, agree with this investigator that the possibility must be considered that the largest portion of the drug may be burned in the body, and perhaps to a lesser degree with La Rue in his conclusion that all of the drug is oxidized within 15 hours.

In a recent paper³ we reported an increase in the amount of non-fermentable reducing substances in the urine of dogs which had received paraldehyde, stating that it appeared probable that the latter formed part of this increment. The amounts of paraldehyde per cc. of urine shown in Table 2 would seem to confirm this belief, since their increases approximately parallel those of the urine non-fermentable reducing substances observed in the earlier report.

It is felt that a suitable clinical method should be developed for the determination of paraldehyde in blood, and that its utilization in the study of the blood paraldehyde level over a continuous period of 24 to 48 hours would yield important information on the therapeutic effects, dosage, excretion and fate of this drug.

Summary and Conclusions. 1. The excretion of paraldehyde by the lungs, in dogs anesthetized with this drug, showed a progressive increase during the first 4 hours, reaching an average level at that time which remained approximately the same for the 3 following hours of continuous observation. Excretion by this route fell off sharply during the next 17 hours, and was practically negligible at the beginning of the second 24-hour period. The amount estimated to be excreted by the lungs during 7 hours was relatively small, averaging only 2.8% of the total amount administered.

2. Excretion of paraldehyde by the kidneys in the same animals during a 7-hour period averaged 1.3% of the total administered and fell off sharply during the next 17 hours, being negligible after that time.

3. The amount of paraldehyde excreted in the urine from the third to the seventh hours, and perhaps later, was proportional to the amount of urine; its elimination by this route can therefore be hastened by increasing the output of urine.

4. Paraldehyde forms the increment in the increase of non-fermentable reducing substances in the urine observed in earlier investigations.

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OBSERVATIONS ON THE ETIOLOGY OF ULCERATIVE COLITIS.

IV. THE RECTOMETROGRAM AND THE RECTAL REACTIONS OF EIGHT NORMAL SUBJECTS AND ONE PATIENT WITH ULCERATIVE COLITIS BEFORE AND AFTER SPINAL ANESTHESIA.

A PRELIMINARY REPORT.

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IN order to study the activity of the rectum in humans an attempt was made to develop a uniform method similar to the cystometrogram which has been used so advantageously for observations on the bladder.⁶ The purpose of such a test is to measure the responses of the rectum to a fixed stimulus and thus to compare the rectal reactions in the same subject under various conditions as well as in different subjects under the same circumstances. Since the rectum is not a closed cavity it is obviously impossible to study its movements by introducing fluid alone as one does with the urinary bladder. It has been found by previous investigators^{2,3,7} that rectal movements can be studied by introducing a balloon tied over the

end of a catheter into the rectum and distending it with a fluid medium. Such a system can be connected to a kymograph or a manometer.

Methods. The distal 7.5 cm. of an ordinary latex condom was tied over the end of a No. 16 French rubber catheter. Three thicknesses of condom were used in order to give it the necessary resistance. This balloon was lubricated and inserted into the rectum through a proctoscope which was 12.5 cm. in length. A long sponge forceps was used to grasp the tip of the balloon which was placed at the inner end of the proctoscope just against the rectal wall. While this position was maintained with the forceps the proctoscope was withdrawn. The forceps were then spread apart and removed. The patient was instructed to assume a comfortable position in bed, to breathe evenly and not to move or talk throughout the examination. The reason for this is that any bodily movements, irregular breathing or talking affect the rectal pressure and hence tend to give false results.

The balloon held 50 cc. of water before it evidenced any internal pressure, and this amount of water was added slowly, after which the catheter was connected to a water manometer. The system contained a side arm through which additional water could be added at regular intervals. At first, 10 cc. of water were added every 3 minutes, but later a change was made to 10 cc. every 2 minutes in normal subjects. This change was made because in 1 normal individual the 3-minute injections failed to elicit any rectal contractions, whereas the 2-minute injections produced contractions in all subjects studied without spinal anesthesia. In the patient with colitis 3-minute injections were made at all times. The injections were continued until the balloon contained 150 cc. of water.

During the injection of water the column in the manometer rose approximately 20 cm. and after injection fell at once to a certain level where it remained for a few seconds. This level was taken as the reading for the immediate response of the rectum to injection. If the column rose thereafter above the regular level for the respiratory excursions it was recorded as a rectal contraction and the exact height of the column noted. If there were no contractions, minute readings were taken. The respiratory excursions varied from $\frac{1}{2}$ to 1 cm. and for all readings the lowest level of the excursion was chosen.

After each experiment the balloon was removed from the rectum and connected with the water manometer. Water was introduced in amounts identical with those used when the balloon was in the rectum. In this manner the curve of the pressure within the balloon was determined.

Five normal subjects and 1 patient with chronic ulcerative colitis were studied before and after spinal anesthesia by the method outlined above. In addition, 3 normals were observed without spinal anesthesia and 3 others studied after spinal anesthesia without control observations. In the patient with chronic ulcerative colitis 5 control observations were made and spinal anesthesia was administered on 6 different occasions. The level of anesthesia varied in the patients studied but in all instances was at or above the level of the iliac crest.

Results. With the balloon in the rectum the level to which the manometer fell after each injection was usually slightly higher than that of the balloon alone for the same volume. During the ensuing 2 minutes, however, it tended to fall to the level of the balloon. In addition to this immediate response of the rectum, there occurred in all 8 normal subjects without spinal anesthesia a series of rectal

contractions. Considerable variation was encountered in the normals as to frequency and height of contractions but the various types of curves will not be discussed in this communication. Figure 1 shows the curve of a normal subject.

Figure 2 shows the results in the same subject after spinal anesthesia. It was a constant finding in all 8 patients that after spinal anesthesia the initial rise after each injection was still present but there were no additional rectal contractions. In the normal subject without anesthesia, there was a subjective sense of fullness or desire to defecate whenever a rectal contraction was noted. Under spinal

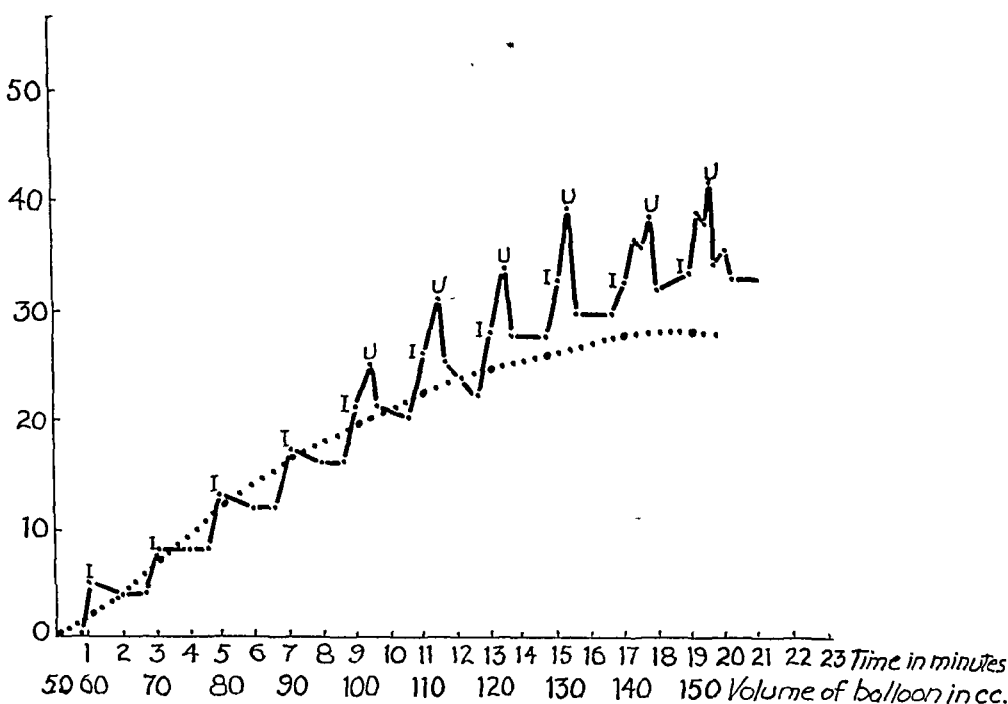


FIG. 1.—Rectometrogram in a normal subject before spinal anesthesia. The heavy black line is the record of the manometric reading with the balloon inside the rectum; the dotted line of the balloon outside the rectum. I. indicates the level to which the water column fell after each injection of water; U. a subjective urge to defecate as noted by the patient. These symbols are the same in all figures.

anesthesia the subjects experienced no subjective sensation whatsoever.

In the patient with chronic ulcerative colitis the initial rise after injection was also present. The rectal contractions were quite frequent and of a much higher order than those noted in the normal. Figure 3 shows one reading taken on this patient without spinal anesthesia. Accompanying each contraction or series of contractions there was a subjective sensation of tenesmus and urgency.

When spinal anesthesia was administered to this patient there were fewer contractions than without anesthesia but their height

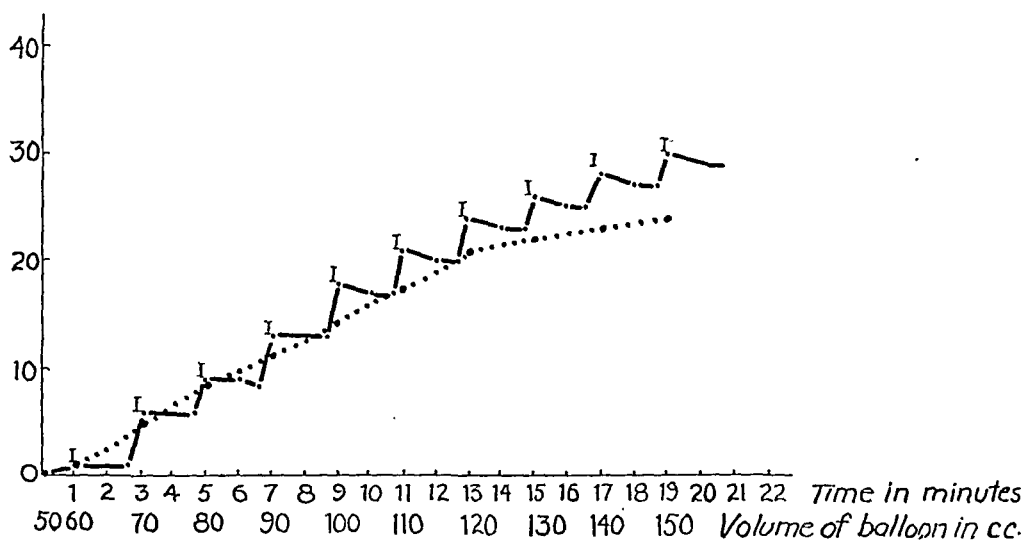


FIG. 2.—Rectometrogram in a normal subject after spinal anesthesia. This is in the same subject as Figure 1.

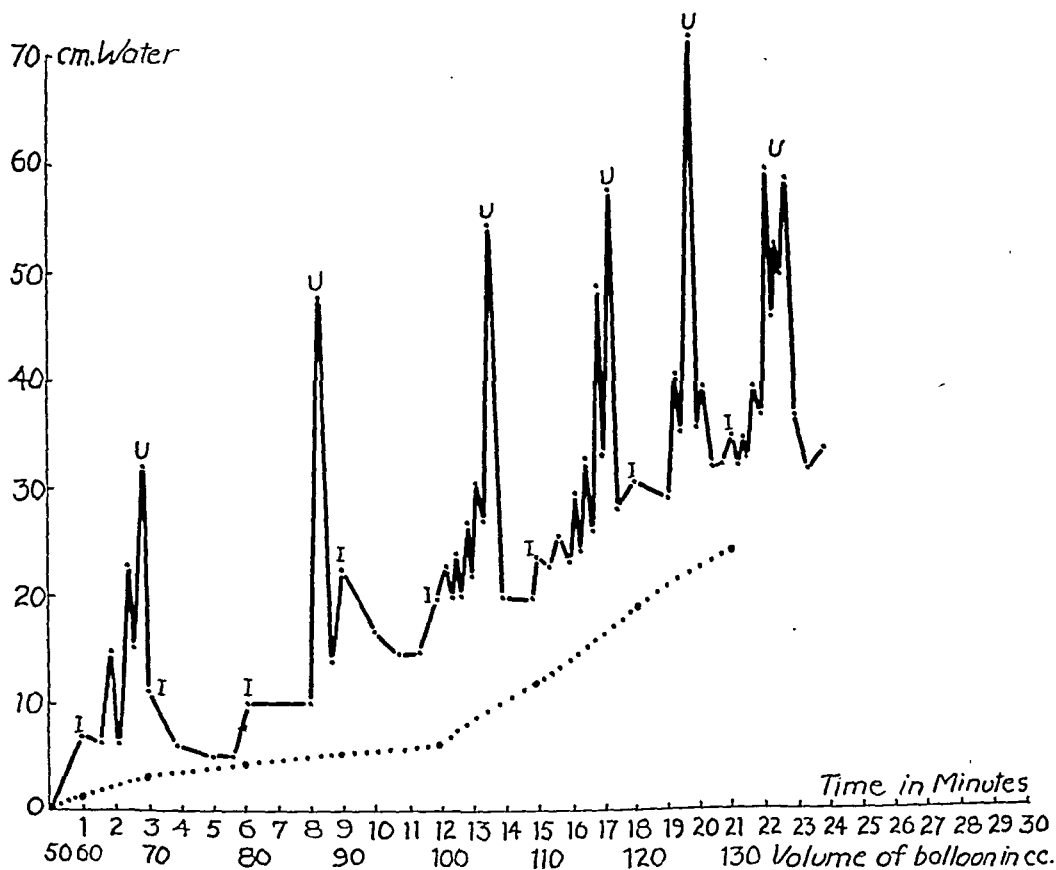


FIG. 3.—Rectometrogram of a patient with chronic ulcerative colitis at a time when he was having 15 movements a day. The observations were discontinued at 130 cc. because of the severe tenesmus and urgency.

remained unchanged. Under anesthesia the patient had no subjective sensation of the contractions. Spinal injections were made on 6 different occasions with the level of anesthesia varying from the iliac crest to the nipples and in each instance there occurred rectal contractions, although their actual number varied from time to time. Figure 4 shows a curve after spinal anesthesia in this patient 2 days after Figure 3 was obtained. One constant result noted in the patient with colitis was the absence of bowel movements during the presence of anesthesia.

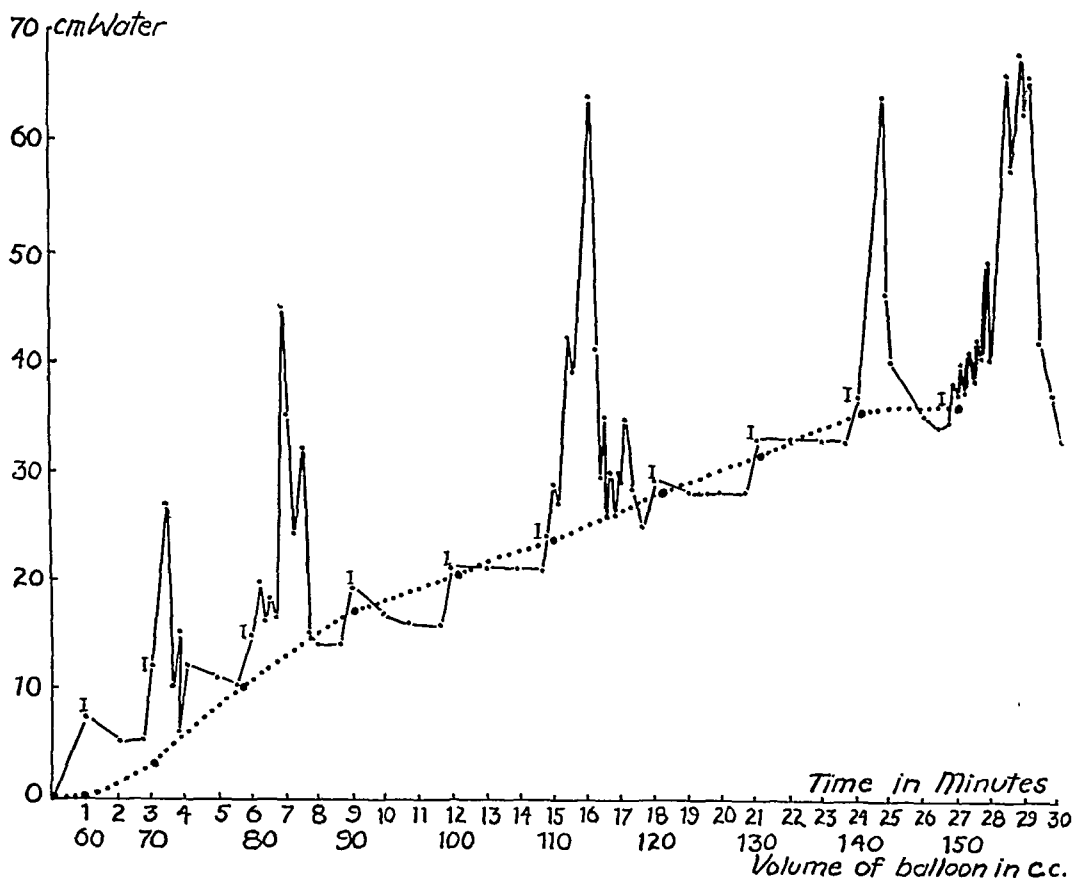


FIG. 4.—Rectometrogram in same patient as Figure 3, after spinal anesthesia. The number of the contractions is diminished but their character is not changed.

Discussion. From the foregoing observations one can say that in normal subjects the rectal muscles evidence two types of response to stimulation by distention with a balloon. The first type of reaction is an immediate increase of rectal pressure after each injection of water into the balloon. This response is present both before and after spinal anesthesia and is therefore a local response. Whether this is a reaction of smooth muscle to stretching or to a short reflex arc through the myenteric plexus cannot be stated with certainty.

The reader is referred to the discussion by Alvarez¹ on this as yet unanswered problem in physiology.

The second type of contraction is that of a rectal response superimposed upon the increased tone that occurs after the injection of water. Such contractions occur with considerable variation in number and height but they were found in all normal subjects with the method used. Similar contractions were noted by Hines, Lueth and Ivy³ in normal subjects and by Denny-Brown and Robertson² in patients with complete transection of the spinal cord at various levels. They are therefore probably due to a reflex arc through the spinal cord which may or may not reach the conscious level, depending upon the continuity of afferent pathways through the cord.

In the patient with ulcerative colitis, there were severe rectal contractions present on each of 5 control observations and on each of 6 occasions when spinal anesthesia was administered. This points to a hyperactive local response of the muscle. Although the number of contractions was reduced under spinal anesthesia in this patient, the important fact remains that powerful contractions, not found in any of 7 normals either before or after spinal anesthesia, still remained in the patient with ulcerative colitis.

This finding may well have an important bearing on the chronicity of ulcerative colitis once the disease process commences. It has been shown elsewhere⁴ that spasm and hypermotility of the colonic muscles in an explant of dog's colon produce the same gross and microscopic changes as are observed in early ulcerative colitis. In another communication,⁵ it was noted that the lesions of ulcerative colitis are distributed according to a muscle pattern. These observations suggest strongly that this condition is due to the intense muscular spasm and hypermotility of the colon which are such prominent clinical features of the disease.

If muscular spasm of the colon may produce severe damage to the mucous membrane, any mechanism that makes for continued overactivity of the muscles tends to perpetuate the process. From the present experiments, it would seem that at least in this particular patient there resides within the muscle of the colon a mechanism which is capable of leading to severe spasm of the muscles in response to local stimuli. The sequence of events leading up to this situation is not understood at present but by means of the rectometrogram and spinal anesthesia it should be possible to study colitis in all of its stages and determine the mechanisms involved in various diarrheas and their progress toward chronicity and/or healing.

Summary. 1. A method for measuring rectal reactions to fixed, measurable stimuli has been described. This is referred to as the rectometrogram and is quite similar to the much-used cystometrogram.

2. In a group of 8 normal subjects the rectometrogram showed two

types of contractions in response to stimulation. The first was an immediate increase in rectal tone after each injection of water into the balloon, and the second was a contraction of the rectum occurring between injections. The second type of contraction disappeared under spinal anesthesia. The first type of contraction is probably a local response and the second a reflex through the spinal cord.

3. In a patient with ulcerative colitis the rectal contractions were much more powerful and more prolonged than those noted in the 5 normal subjects. These contractions were lessened in number but were not influenced in character by spinal anesthesia on 6 different occasions. This argues for a mechanism independent of the spinal cord as responsible for these contractions. The importance of these contractions on the chronicity of ulcerative colitis has been discussed.

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BOOK REVIEWS AND NOTICES.

ALLERGIC DISEASES. Their Diagnosis and Treatment. By RAY M. BALLYEAT, M.A., M.D., F.A.C.P., Associate Professor of Medicine and Lecturer on Diseases due to Allergy, University of Oklahoma Medical School; Chief of the Allergy Clinic, University Hospital, etc. Assisted by RALPH BOWEN, B.A., M.D., F.A.A.P., Chief of Pediatric Section, Ballyeat Hay Fever and Asthma Clinic, Oklahoma City, Okla. Pp. 547; 145 illustrations, including 8 in color. Fifth edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1938. Price, \$6.00.

MUCH useful and practical material. The Reviewer, however, sharply condemns the author's extensive use in asthma of endolaryngeal instillation of iodized oil and particularly the delegation of such instillation to the patient himself. R. K.

SILICOSIS AND ASBESTOSIS. By VARIOUS AUTHORS. Edited by A. J. LANZA, M.D., Assistant Medical Director, Metropolitan Life Insurance Company; Chairman, Industrial Hygiene Committee of the New York Tuberculosis and Health Association. Pp. 439; 61 illustrations. New York: Oxford University Press, 1938. Price, \$4.25.

THIS volume probably contains more general information concerning the medical and public health aspects of silicosis and asbestosis than any other single volume published in this country. The 7 chapters are each written by an authority in the field being discussed.

Chapter I is a historical review of the entire subject by R. R. Sayers and A. J. Lanza, who also collaborated in Chapter II, on the etiology of silicosis and asbestosis. The importance of the clinical signs and symptoms in these diseases is considered and the more common findings are tabulated in outline form.

Chapter III, the longest in the book, on the Roentgen ray diagnosis of silicosis and asbestosis, is by E. P. Pendergrass. The first portion of the chapter contains a review of the anatomy and dynamics of the healthy chest. After discussing these fundamentals, the author concerns himself with a detailed description of the roentgen manifestations of silicosis and asbestosis. The typical roentgen appearances in simple silicosis and silicosis with infection are described and their histologic significances tabulated. The value of the clear verbal description is enhanced by roentgen reproductions.

The pathology of silicosis and asbestosis is presented by S. R. Gloyne in Chapter IV. The gross and microscopic appearances of the more common lesions are clearly defined and well illustrated. Complications such as tuberculosis, non-tuberculous infections and cancer are also considered.

The contributions of the experimental pathologist are presented by L. U. Gardner in Chapter V. In it, one finds a complete review of experimental methods used in the study of tissue responses to silicious and non-silicious dusts.

The occupational, preventive, and legislative aspects of pneumoconioses are extremely well handled by E. L. Middleton in Chapter VI. The author describes the more common dust hazards outlining the accepted procedures for the prevention of pulmonary damage in various industries. Most of the references pertaining to compensation legislation is of English origin but as they are discussed in broad terms, find application to similar problems in the United States.

Chapter VII considers the economic and public health aspects of silicosis and asbestosis. The author, A. J. Lanza, summarizes the outstanding problems concerning dust control which face us today. His remarks concerning the rôle of the United States Public Health Service, engineers, and physicians in preventing pneumoconioses are most poignant.

The book is extremely well documented. Each chapter contains an excellent bibliography. The publishers have used a good grade of paper and rather large type. Anyone interested in pneumoconioses will find this book well worth having.

E. P.

SCARLET FEVER. By GEORGE F. DICK, M.D., D.Sc., Professor of Medicine, University of Chicago; Attending Physician, Billings Memorial Hospital, etc., and GLADYS HENRY DICK, M.D., D.Sc. Pp. 149; 8 colored plates and 4 charts. Chicago: The Year Book Publishers, Inc., 1938. Price, \$2.00.

THIS handy little volume offers a very satisfactory survey of our present knowledge of scarlet fever. In addition to the usual presentation of data on etiology, clinical picture, diagnosis, treatment and prophylaxis, there are chapters on the preparation of scarlet fever toxin, specificity of hemolytic streptococci, allergy, antibacterial immunity, local immunity and oral immunization. There are 8 color plates to illustrate the appearance of skin and tongue, the blanching test, skin reactions and specificity tests. The book should have a wide appeal and usefulness.

R. K.

SYMPTOMS OF VISCERAL DISEASE. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Medical Director, Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, Calif.; Professor of Clinical Medicine, University of Southern California, etc. Pp. 442; 87 illustrations and 10 color plates. Fifth edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$5.00.

A DISCUSSION of the anatomy, physiology and pathologic physiology of the vegetative nervous system. The anatomy is particularly well covered. There are, however, some omissions of important recent work in this field. Thus no mention is made of surgery on the sympathetic system in hypertension, and the carotid sinus and the carotid sinus reflex do not appear in the index. Of the 341 cited references only 74 are publications since 1924 (third edition) and only 30 of the 74 appeared since 1929 (fourth edition).

R. K.

PHYSICAL DIAGNOSIS. By RICHARD C. CABOT, M.D., Professor of Clinical Medicine Emeritus in Harvard University; formerly Chief of the West Medical Service at the Massachusetts General Hospital, and F. DENNETTE ADAMS, M.D., Instructor in Medicine in the Harvard Medical School, Courses for Graduates; Associate Physician at the Massachusetts General Hospital. Pp. 846; 391 illustrations. Twelfth edition. Baltimore: William Wood & Co., 1938. Price, \$5.00.

A BOOK which has been a standard text since its first appearance in 1900 needs no introduction. Nor would its 12th edition need a review, were it not that there has been a marked departure from the policy by which the author was guided in previous editions, namely, the inclusion only of material and methods with which the author is personally familiar. Feeling that no one man could be master of all that modern medicine requires shall

be brought to the attention of students of physical diagnosis, the author has not only associated with him a junior author, but has freely consulted with various colleagues on the staff of the Massachusetts General Hospital—the names of 83 are mentioned in the preface. The result is a volume, entirely rewritten, 50% larger and correspondingly more comprehensive and more valuable than its predecessor.

R. K.

THE VITAMINS AND THEIR CLINICAL APPLICATION. A Brief Manual. By PROF. DR. W. STEPP, Director of the I. Medical Clinic, University of Munich; DOZ. DR. KÜHNAU, Director of the Municipal Institute for Balneology and Metabolism, Wiesbaden, and DR. H. SCHROEDER, Associate at the I. Medical Clinic, University of Munich. Translated by HERMAN A. H. BOUMAN, M.D., Minneapolis, Minn. Pp. 173. Milwaukee, Wis.: The Vitamin Products Company, 1938. Price, \$4.50.

This small volume, arranged in very readable form, is an effective condensation of the most important information concerning the vitamins. The degree of condensation necessary in covering such an extensive field has led occasionally to generalizations which are not entirely accurate, but on the whole the authors have shown laudable restraint in the selection of their material and succeed in presenting the most modern point of view concerning the rôle of the vitamins in clinical medicine. The translation has been very well done.

K. E.

CAUSE AND PREVENTION OF DISEASE. By WILLIAM HARVEY PERKINS, M.D., Professor and Director of the Department of Preventive Medicine and Director of the Hutchinson Memorial Clinic, The Tulane University of Louisiana, New Orleans, etc. Pp. 713. Philadelphia: Lea & Febiger, 1938. Price, \$7.50.

It is a truism that prophylaxis should assume a steadily increasing importance in the medical practice of the future. The teaching of preventive medicine is therefore becoming an increasingly important problem in medical pedagogy. The very term "preventive medicine" is broadening in significance from the earlier concept of public health measures and mass sanitation to include every aspect of disease prevention in the individual. It is still debatable as to what is the best method to teach the new preventive medicine. In the Reviewer's opinion the best results will not be achieved until every teacher in every branch of clinical medicine and its specialties shall think, teach and write with prophylaxis constantly in mind. (Certainly the majority of current medical texts are decidedly deficient in this regard.) In addition it is desirable—perhaps necessary until both students and clinical teachers accord to prophylaxis an attention proportionate to its importance—that formal instruction in preventive medicine be a part of the medical curriculum. The best results will be obtained when the teacher is one who by interest and training is qualified to be placed at the head of a department of preventive medicine in which investigation and research shall lend a vital interest to the subject. The author, faced with the task of organizing a course in preventive medicine, found no medical work that contained an inclusive review of the known causes of disease. His efforts to make readily available for students an extensive material scattered in many sources have resulted in this very important textbook. The causes of disease are considered under 6 categories: 1, the inherited factors; 2, defects of nutritive elements; 3, exogenous chemical agents; 4, physical forces and energies; 5, the processes and effects of invading organisms; 6, psychobiologic and biosocial factors and their effects. At the

end of each section are discussed the known methods of defense. The presentation is concise, lucid and interesting. There are few inaccuracies, even for a first edition (*e. g.*, diabetic heredity is wrongly classified as a dominant characteristic). The material on prevention at times appears too skimpy, but then the volume was planned for students, and not primarily as work of reference. The book is welcomed as a valuable addition to medical texts, and is warmly recommended to practitioners as well as teachers and students.

R. K.

WILLIAM B. WHERRY, BACTERIOLOGIST. By MARTIN FISCHER. Pp. 293; 21 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.00.

THE book, beautifully bound and superbly printed, does justice to one whose life span of 62 full years was, for the most part, spent in adversity, but which bore much sound fruit. Born of poor, missionary parents in Ludhiana, India, young Wherry's early life was a struggle for existence, as well as for an education. His success was an indication of the sturdy stock of which he was made and it was this quality which so admirably carried him through the professional training of "the old school." His thorough training exemplified itself in his work and his publications. Although his publications numbered 82 and dealt with widely diversified subjects, it was always out of the commonplace that he was to extract his pearls. He belonged to that generation of bacteriologists who grew up with the science, but contrary to the impression which the book would convey, he was not the last nor the greatest. His broad field of experience, his intimate acquaintance with human nature and his sense of humor, together with the interesting way in which the story is told, should make the book enjoyable and profitable to the reader.

H. M.

BIOLOGY AND PATHOLOGY OF THE TOOTH AND ITS SUPPORTING MECHANISM.

By BERNHARD GOTTLIEB, Research Professor, Columbia University Dental School, etc., and BALINT ORBAN, Assistant Professor, Northwestern University Dental School, Chicago, etc. Translated and edited by MOSES DIAMOND, Associate Professor, Columbia University Dental School, New York; Head of Dental Anatomy Department. Pp. 195; 166 illustrations. New York: The Macmillan Company, 1938. Price, \$5.00.

THE scientific background and experience of the authors render them preëminently fitted to present the subject matter of this book. The dental profession is indebted to Gottlieb for a new concept of the biologic relation of the tooth and its investment structures, whereas much of Orban's work has contributed greatly to further emphasize and clarify Gottlieb's work.

Although the biologic and therefore the pathologic relations of the teeth and their surrounding tissues are not as yet fully understood, many observations are recorded and deductions presented which are valuable to the practitioner in his approach to the pathologic conditions in question. Where these conditions are based on neglect of oral hygiene, a hopeful prognosis is held out. If more emphasis were placed on the treatment of parodontal disease the effect of the text on the routine procedures of practice might prove greater.

It seems to us that the biologic section of the book is more comprehensively presented than the pathologic. The subject matter of "parodontal pyorrhea" and "diffuse atrophy" might have been better illustrated. We do not approve of the statement: "Anti-infection vitamin A, as well as perhaps vitamin C, might be safely administered in the control of the

general predisposition to inflammation." The separate consideration of "traumatic occlusion" is very instructive.

We regret Gottlieb's nomenclature. We should not like to see the term "Schmutz Pyorrhea" introduced in our professional language, and do not believe that it may be used synonymously with gingival inflammation. The reproduction of the roentgenograms is poor, and the unglazed paper does not do justice to the excellent photomicrographs. The addition of a German-English glossary of dental terms used in the original text seems superfluous.

H. C.

LES ÉPIDÉMIES ET LES PERTURBATIONS ÉLECTROMAGNÉTIQUES DU MILIEU EXTÉRIEUR. By PROF. DR. A.-L. TCHJEVSKY. Pp. 239; 120 illustrations. Paris, Éditions Hippocrate, 1938. Price, 40 fr.

IN the year 1876 the Russian-Austrian meteorologist Koeppen called attention to the association that seemed to exist in the periodicity of certain human mass reactions and the climatic periodicity which we roughly associate with the sun spot cycle, or its multiples.

Of course the association of epidemics and epizootics with terrestrial disturbances (earthquakes, floods, severe storms, etc.) was one of the most widespread popular beliefs in the ancient world, but naturally fell into discard with the advent of bacteriology. Nevertheless recent decades have made evident that epidemic phenomena cannot be explained wholly on the basis of the invading organisms; it has become evident that the waxing and waning of epidemics involve the human soil as well, and the human soil involves terrestrial factors and in turn more remote cosmic factors. A number of investigators have turned to study the effect of possible electromagnetic phenomena in this connection, because of the obvious terrestrial electromagnetic disturbances that are associated with solar disturbances when sun spot activity is accentuated.

This book represents the most recent of these studies. In it the author first discusses the general thesis, describes solar activity and the terrestrial reflection in electromagnetic phenomena, and reviews the historical background of human epidemiologic experience. In this connection he naturally analyzes the different climatic cycles that have been described. In Chapters 6 to 15 the author takes up the possible correlations that exist between oscillations in electromagnetic activity and the various human maladies, among them Asiatic cholera, influenza, recurrent fever, plague, diphtheria, meningitis and poliomyelitis, malaria, typhoid fever and dysentery, English sweat, scarlet, rheumatism, tuberculosis, and so on. Naturally he makes use of Russian statistics to a great extent, although he considered other material as well. Perhaps the most striking observations are those that deal with meningitis, where a fairly clear-cut correlation can be observed with statistical data covering more than a century.

There can be no valid objection to any of the material presented in these chapters, though obviously the historical record and the statistical material is at best not absolutely reliable. Having revealed an association with sun spot activity, with increasing or decreasing phases of the diseases so far discussed, he then takes up in Chapter 14 the prediction of epidemics, and in the final chapter discusses the possibility of the influence of electromagnetic bombardment on microorganisms, assuming that bombardment by negative or positive ions may be factors in altering the invasiveness or the toxicity of the microorganisms.

The presentation is useful in offering an approach to an intricate problem but it has serious handicaps:

Granted that an association can be established between sun spot activity and epidemic periodicity it by no means follows that the effective factor is directly due to an electromagnetic change in the human environment.

Actually we have no clear-cut evidence that electromagnetic forces have any effect whatsoever on the human being. As far as can be determined the major environmental factors (air mass, sunshine, diet, fatigue, and so on) so far outweigh any possible electromagnetic forces that it has not been possible up to the present time to determine by physiologic methods the response to naturally occurring electromagnetic disturbances. The author's presentation therefore involves a purely hypothetical explanation.

Secondly, we have no actual observation establishing the probability that the invading organisms are so influenced.

Finally, we must keep in mind that with sun spot periodicity the entire air mass environment of the human group becomes more variable (rainfall, temperature, and so on) and that with greater variability of the environment the physiologic condition of the population presents corresponding variability, and that with greater variability the probability exists that there will be greater fatigue and lessened resistance.

If, therefore, the initiation of an epidemic involves lessened resistance of human population rather than actual alteration of bacterial population, sun spot periodicity, reflected in greater strain on the population, may be actually associated in epidemic phenomena, not because of electromagnetic phenomena *per se*, but because the population at certain phases of the sun spot cycle may be relatively more alkaline and resistant, let us say, or more acid (fatigue) and susceptible to infectious diseases in general.

Certain the problem is not as simple as the author's contribution might lead us to believe; all of which does not detract from the desirability of further study along the lines that he has so far followed.

W. P.

A MANUAL OF FRACTURES AND DISLOCATIONS. By BARBARA BARTLETT STIMSON, A.B., M.D., MED. SC.D., F.A.C.S., Associate in Surgery in the College of Physicians and Surgeons, Columbia University, New York City; Assistant Attending Surgeon to the Presbyterian Hospital, New York City. Pp. 214; 95 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$2.75.

THE author's handbook is particularly intended for medical students and for general practitioners as a brief guide for the treatment of fractures and dislocations. She writes clearly and with the understanding of one whose experience has been great in this specialized field.

The book begins with a short section on general considerations, the importance of the clinical diagnosis, an accurate and full history and a careful painless physical examination. She discusses briefly, but clearly, the accepted theories of fracture healing and describes the principles of the emergency treatment of fractures, the reduction by the use of traction in the treatment of compound fractures and the rehabilitation of fractures. She then takes up in order, fractures of the various parts of the body, with brief discussions of occurrence, displacement, diagnosis, pathology, treatment, time of immobilization and prognosis. Each section is illustrated with diagrammatic line drawings which clearly demonstrate the statements made in the text. No Roentgen ray pictures are reproduced but tracings of Roentgen ray show very clearly the displacement and the value of the methods of treatment which are recommended.

The treatments described are those used by the fracture service at the Medical Center in New York. Open reduction is recommended if closed reduction is unsuccessful. The author does not recommend the use of the walking iron and plaster cast in fractures at the ankle.

The brevity of the book can be judged from the fact that only two short paragraphs, a part of a single page, is given over to the question of internal splinting by nails for fractures of the neck of the femur.

The author has given us a book which should be of particular value to those who occasionally have to meet the problem of treating fractures; it is practical in every sense of the word. In it, in a few minutes, can be found information which may serve to describe the principles and the commoner methods of treating fractures. It can be construed as answering its author's wish—to give a brief book, for the use of medical students and general practitioners, which would give them the essentials without the necessity of wading through a considerable amount of the detailed information which may be demanded from an expert.

L. F.

THE WHEEL OF HEALTH. A Study of a Very Healthy People. By G. T. WRENCH, M.D. (LONDON). Pp. 146; 1 illustration. London: The C. W. Daniel Company, Ltd., n.d. Price, 6/-.

In this small monograph the author develops the thesis that many of our ills are due to the food which we eat, or more accurately which we do not eat. He believes that the diet of the average inhabitant of England contains foods that are too highly refined and not enough uncooked foods. These opinions are based largely upon a second-hand study of the people of Hunza in Northwestern India who, according to Sir Robert McCarrison and other visitors to this section of the world, are an exceptionally healthy people. The idea is expressed that not only is it a question of the particular foods which are eaten but also the manner in which these foods are raised. In the words of the author "These three transferences—soil to vegetable, vegetable to animal, animal and vegetable back to soil—form the eternal wheel of health."

J. J.

INFECTIONS OF THE HAND. A Guide to the Surgical Treatment of Acute and Chronic Suppurative Processes in the Fingers, Hand and Forearm. By ALLEN B. KANAVAL, M.D., Sc.D., Late Professor of Surgery, Northwestern University Medical School, Chicago, Illinois; Attending Surgeon, Wesley Memorial and Passavant Memorial Hospitals, Chicago. Pp. 503; 229 illustrations (many in colors) and 1 colored plate. Seventh edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$6.00.

It seems very fitting that one of the author's last acts should have been the revision of his most well-known work on infections of the hand. This sixth revision and seventh edition of his monograph contains a further summary of his vast experience in this field of surgery.

The early chapters show the same painstaking anatomical studies as the previous editions of this monograph. However, he has added a chapter on the prophylactic treatment of injuries and a study of the treatment of hand infections among employees. He has also amplified the chapters on infection of the superficial tissues of the hand, such as carbuncles, erysipeloid, blastomycosis and so forth. The chapter on infections about the metacarpophalangeal joint reproduces again the colored plates of the work of Koch and Mason. A more complete chapter on the gangrenous infections (streptococcic, symbiotic and gas gangrene) has been added, largely from the publication of Meleney and also detailing the author's experience in the treatment of these lesions. In the latter part of the book are chapters on the sequelæ and after treatment of infections of the hands, in which there are discussed the methods of caring for cases with marked contracture. In addition, various specialized apparatus and types of physiotherapy to improve function after a neglected infection are discussed.

This book still remains one of the outstanding works on this important

subject in surgery. It may well remain as a monument to the industry and scientific interest displayed by the author in his preparation for the profession of a most painstaking description of these lesions with detailed instruction as to their treatment.

It is unfortunate that the author's experience did not permit him to give more space to the use of sulphanilamide in many of these infections. The drug is merely mentioned with the statement that results have been good but that his experience has not been sufficient to permit any very detailed description of its use.

The illustrations remain a model for this type of text, many in color and many diagrammatic with colored inserts, to show clearly the points the author brings out in the text.

This last edition should be in every library and in the hands of every surgeon who attempts to treat infections of the hand. L. K. F.

A TEXTBOOK OF MEDICAL BACTERIOLOGY. By DAVID L. BELDING, M.D., Professor of Bacteriology and Experimental Pathology, Boston University School of Medicine, and ALICE T. MARSTON, PH.D., Assistant Professor of Bacteriology and Immunology, Boston University School of Medicine. In collaboration with SANFORD B. HOOKER, SIDNEY C. DALRYMPLE, JOSÉ P. BILL and MATTHEW A. DEROW. Pp. 592; 41 illustrations, 46 tables and 1 colored plate. New York: D. Appleton-Century Co., Inc., 1938. Price, \$5.00.

THIS abortive piece of work which cannot truthfully be called a textbook of medical bacteriology, should be discouraged before its inadequacies seriously handicap the students for whom it was intended. Though the authors prepared the book for medical students and practicing physicians, it would not fill the needs of a high school text, where in the study of botany it might be desirable to expose the students to a smattering of that phase of botany called bacteriology and especially to those microorganisms which play a part in our every day life. No teacher, after reading the first paragraph of the preface, would select the work for a textbook. The authors exhibit their short sightedness as teachers and also as authors in an opening paragraph that states that they have presented only one aspect of controversial subjects. The fields of biology and medicine contain so many controversial subjects that any book which presents only one aspect of a controversy is very likely to be out of date in many respects before it is ready for distribution. Leading students to a wrong impression is as serious as teaching a falsehood.

The table of contents presents a fair outline for a textbook but the elaboration of the outline is disappointing. Scope has been sacrificed to convenient size, but practically any other textbook of similar size on the same subject is far superior, and many of them have enjoyed the additional refinement of numerous revisions with time. Considerably less than one page has been devoted to scarlet fever. Four lines have been devoted to septic sore throat and even less space than that to endocarditis. No mention at all is made of chemotherapy.

There are 45 illustrations. Some are incomplete and others misleading. A few photo-micrographs would have served the purpose much better, as the facts would have been presented as they were and not as an artist's interpretation. References were left out purposely, but thirty-two choice supplementary references have been listed near the back of the book—even these show poor choice and carelessness on the part of the authors. One book cited is out of date by three editions. That section of the appendix pertaining to special methods of staining is comprised of two methods for

staining capsules, one for staining flagella, three for staining the metachromatic granules in the diphtheria bacillus (which the authors persist in referring to throughout the book as the diphtheric bacillus) and two for staining spirochetes. The section is obviously inadequate. No mention is made to such important stains as Gram's or Ziehl-Neelsen's or Loeffler's stain, which has proven its worth and remained unaltered through more than fifty years of constant use.

The thirteen page index is entirely inadequate. Names of diseases are not listed; so the book would be very impractical for students or practicing physicians if they wished to consult it for immunologic or bacteriologic information pertaining to specific diseases or infections. Even important diseases such as whooping cough, scarlet fever, smallpox, etc., *ad infinitum*, are not mentioned in the index. The information which a medical student needs to know is missing from this book. It would be a detriment for such a student to use the book as a text and a practicing physician would have no use for it whatsoever.

H. M.

CLINICAL AND EXPERIMENTAL INVESTIGATIONS IN AGRANULOCYTOSIS. With Special Reference to the Etiology. By PREBEN PLUM. English Translation (from the Danish) by HANS ANDERSON, M.D. Pp. 410 125 illustrations (many in color). London: H. K. Lewis & Co., Ltd., 1937.

THIS splendid monograph from Copenhagen is a complete, well written, well translated and well documented account of the clinical and experimental background and present status of that strange twentieth century disease or syndrome generally known as agranulocytic angina. Plum's personal contributions to the subject have been noteworthy. Denmark has, as far as the Reviewer knows, the unique position of having reduced its consumption of aminopyrine from a peak level of 2400 kilograms in 1934 to 400 kilograms in 1936 with a concomitant reduction in the reported cases of agranulocytic angina from 30 in 1934 to 9 in 1936. The table of contents and the chapter titles and subtitles help to compensate for lack of an index. The microphotographs and charts are good and the bibliography (422 references) is well chosen. More than one-third of the references are from the American literature. While the main thesis of this monograph (the drug-etiology of agranulocytosis) is still *subjudice* in the minds of some, there is here presented the best and most complete picture of this dramatic malady available today.

T. F.-H., Jr.

UROLOGY. By DANIEL N. EISENDRATH, M.D., Consulting Urologist to The American Hospital, Paris, France; Formerly Attending Urologist, Michael Reese and Cook County Hospitals, etc. and HARRY C. ROLNICK, M.D., Attending Urologist, Michael Reese, Mt. Sinai and Cook County Hospitals, Chicago, etc. Pp. 1061; 750 black and white and 12 colored illustrations, 4th edition. Philadelphia: J. B. Lippincott Company, 1938. Price, \$10.00.

It is a pleasure to welcome the 4th edition of this standard text, and to find numerous changes which recent advances have made necessary.

Subjects of timely import, such as adrenal hyperplasia and neoplasm, and neurologic bladder dysfunction, have been given greater consideration than heretofore. Separate chapters on pediatric and female urology emphasize their importance. An excellent addition to the discussion of surgical nephritis, in this edition, is a résumé of the medical aspects. The

chapters on embryology and anomalies of the genital tract are outstanding in their clarity and inclusiveness.

Excretory urography is discussed with impartiality as to its advantages and drawbacks. The chapters on Diseases of the Prostate, on Operations on the Prostate, on Non-tuberculous and Tuberculous Infections, on Nephrolithiasis, and on Renal Tumors have been rewritten. The subject of venereal infections is adequately covered and illustrated, even though the space allotted to gonorrhea in the male has been reduced. The newer studies of the sex hormones, and their employment in both diagnosis and treatment, have been included. The practical value of the chapters on operative technique is considerable, and has been enhanced by the addition of numerous illustrations.

The book is to be recommended as a valuable single volume text in pre- and postgraduate teaching for its concise and complete presentation of the entire field of urology.

A. R.

BACTERIA. The Smallest of Living Organisms. By DR. FERDINAND COHN (1872). Translated by CHARLES S. DOLLEY (1881). Introduction by MORRIS C. LEIKIND. Pp. 44; 4 illustrations. Baltimore: The Johns Hopkins Press, 1939. Price, \$1.00.

THIS reprint from the Bulletin of the History of Medicine (7, 58, 1939) makes available to a wider circle of readers one of the most important texts in the history of bacteriology. Several years before Koch's classical publication on anthrax and while Pasteur was still studying fermentation, Cohn published his 35-page, paper-bound booklet, that exhibits the considerable knowledge of bacteria that existed at that time. Cohn's division of bacteria into 6 groups is much as we classify them today. His allusions to Leeuwenhoek, Davaine, and Kolb's cholera vibrio (1866) are but a few of the items that show that bacteriology, like the Cell Doctrine and most scientific developments, came into being like the Pyramids and not like Minerva. Reprinting Dr. Dolley's translation has its special interest in calling attention to the valuable contributions of this pioneer in American bacteriology.

E. K.

NEW BOOKS.

Pulmonary Tuberculosis in Adults and Children. By JAMES ALEXANDER MILLER, A.M., M.D., D.P.H., Sc.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Late Chief of, now Honorary Consultant to, the Tuberculosis Service, Bellevue Hospital, New York, and ARVID WALLGREN, M.D., Head of the Children's Hospital, Gothenburg, Sweden. Pp. 196; 77 illustrations. New York: Thomas Nelson & Sons, 1939. Price, \$3.50.

Elektrodiagnostik. By DR. B. NEOUSSIKINE, and DR. D. ABRAMOWITSCH, Tel Aviv. Pp. 242; 30 illustrations. Bern: Hans Huber, 1939. Price, Schw. Fr. 12.

Gross Anatomy. A Brief Systematic Presentation of the Macroscopic Structure of the Human Body. By A. BRAZIER HOWELL, Associate Professor of Anatomy, Johns Hopkins University School of Medicine. Pp. 403; 56 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, \$6.00.

Manual of Toxicology. By FORREST RAMON DAVISON, M.B., M.Sc., Ph.D., Assistant Professor of Pharmacology, College of Medicine, University of Vermont. With a Foreword by DAVID MARVIN, M.D., Professor Emeritus of Pharmacology, College of Medicine, University of Vermont. Pp. 241. New York: Paul B. Hoeber, Inc., 1939. Price, \$2.50.

- Population, Race and Eugenics.* MORRIS SIEGEL, M.D. Pp. 206. Hamilton, Ontario: By the Author, 1939. Price, \$3.00.
- Angina Pectoris.* Nerve Pathways, Physiology, Symptomatology, and Treatment. By HEYMAN R. MILLER, M.D., Attending Physician, Sydenham Hospital; Associate Attending Physician, Montefiore Hospital, New York City. Pp. 275; 39 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$3.25.
- Consultation Room.* By FREDERIC LOOMIS, M.D., Diplomate of the American Board of Obstetrics and Gynecology. Pp. 281. New York: Alfred A. Knopf, 1939. Price, \$2.50.
- Das physikalische Denken in der Geschichte der Medizin.* Prof. Dr. med. et phil. DR. H. C. PAUL DIEPGEN. Pp. 39. Stuttgart: Ferdinand Enke, 1939. Price, Rm. 2.
- Oh, Doctor! My Feel!* By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 116; 3 illustrations and 6 plates. New York: D. Appleton-Century Company, 1939. Price, \$1.50.
- It's More Fun to be Thin.* By JEAN Z. OWEN. Pp. 182; illustrated. Boston: Marshall Jones Company, 1939. Price, \$2.00.

NEW EDITIONS.

- The Wisdom of the Body.* By WALTER B. CANNON, M.D., Sc.D., LL.D., Dr. (Hon.) George Higginson Professor of Physiology, Harvard Medical School. Pp. 333; 40 illustrations. Revised and enlarged. New York: W. W. Norton & Co., Inc., 1939. Price, \$3.50.
- Failure of the Circulation.* By TINSLEY RANDOLPH HARRISON, M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. Pp. 502; 61 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$4.50.
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PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

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RECENT PROGRESS IN THE TREATMENT OF DEAFNESS OF OTOSCLEROTIC ORIGIN.

THERE has been evidenced an increased attention in the literature in the treatment of the impairment of hearing of otosclerosis. Our well known therapeutic impotence when faced by the continued progressively increasing deafness, may in the light of these contributions change to a more encouraging attitude towards these unfortunately deafened patients. In the past, these handicapped individuals could only be advised to either learn lip reading or wear a hearing aid. In 1935, however, Gray³ startled the Otologic Section of the Royal Society of Medicine, by reporting the improvement in hearing and the amelioration of the tinnitus in 7 of 14 cases of otosclerosis treated by the injection of thyroxine through the drum head into the middle ear cavity. In the following year Goldstein² reported his experience with the treatment in 4 cases that received careful audiometric control and concluded that the degree of improvement was variable. In some cases, the reduction of the tinnitus decreased the confusion incident to the tinnitus and so indirectly aided the sound perception and thus rendered more intelligible the comprehension of the ordinary conversation. Our experience, however, has not been encouraging, the indifferent success leading us to discontinue it after a year's trial. A very complete discussion of the value of intratympanic therapy occurred before the Otologic Section of the Royal Society of Medicine¹ in 1937 and was on the whole somewhat lacking in enthusiasm. Of the 11 otologists who took part in the discussion one noted marked improvement in some 80 % of his patients. Others obtained improvement in but a small number of their cases. One report noted an amelioration of the tinnitus in 35 % of the cases observed and increase in hearing as shown by audiometric control in

but 20%. Another found that no sustained increase in hearing that was of practical benefit to the patient could be proven, although partial or complete reduction of the tinnitus was noted by 20% of the patients. Five other otologists concluded that their results were practically negative. The effect of the treatment upon both the hearing and the tinnitus must be interpreted with caution. It is well known that the hearing and head noises in otosclerotic individuals vary with emotional states, the weather and other factors. The rationale of the therapy is also somewhat dubious, as aside from the hyperemia of the middle ear mucosa, no other action upon the pathologic labyrinthine capsule has as yet been proven. Rainisch,⁹ however, has found that otosclerotic individuals had an increase in the deafness when under the influence of epinephrine and an improvement upon the use of pilocarpine. The improvement of hearing could last from 8 to 12 days and could be repeated by further injections of the pilocarpine. He found a parallel reduction in the tinnitus with the improvement of hearing and an increase in the tinnitus with the fall in hearing. Another interesting phase of the response of otosclerotic individuals is noted in the report of Mortimer, Wright, Thomson and Collip⁸ who noted improvement in the hearing of certain of their cases of atrophic rhinitis who also had chronic progressive deafness. They found that they could obtain an increase of hearing varying from 5 to 60 sensation units in certain cases when treated by daily insufflations of 1 cc. of oil containing 1000 international units of estrin. No patient was treated for less than 3 months, many for 6 months and some for as long as 2 years. They carefully checked their results by monthly audiometric tests. They suspect that there may be a hitherto unrecognized "oto-genital" relationship which may play a part in the physiology of hearing. As this report is quite recent, our experience of but 2 months with this form of therapy in 4 cases is probably not significant. These patients have not as yet, however, shown any improvement in their audiometric tests.

Probably of much more interest are the recent attempts to procure a new site in the labyrinth for the reception of auditory vibrations in place of the fixed stapes at the fenestra ovalis which is a major cause of the deafness of otosclerosis. The object of these surgical procedures in the past was to remove the bony covering of one of the semicircular canals so that the underlying membranous canal could receive the vibrations and transmit them via the peri-lymph to the cochlear end organ of the auditory nerve. Practically all of these procedures ended in failure due to filling of the surgical defect with regenerated bone or callus. Sourdille¹⁰ found that the progression of the deafness could be stopped and cessation or diminution of the tinnitus obtained by making such a labyrinthine fistula and that closure of the fistula was followed by recurrence of the progressive hearing loss and an increase or recurrence of the tinnitus. He found further that if the fistula was made large enough and situated in an area where the auditory vibrations could impinge upon it directly, there could be demonstrated a definite improvement over the preoperative hearing. He developed his so-called tympanolabyrinthopexy, which he performed in 3 stages at intervals of several months. He has been able to report success in about 80% of his cases.

Holmgren⁵ utilizing the same principle has developed a technique in which he uncovers the antero-lateral wall of the saccus endolymphaticus and then makes fistulae into the horizontal and posterior vertical semicircular canals, inserting a pad of fat, separated from the exposed membranous canals by gold leaf. He found marked and frequently dramatic increase in the hearing at the time of operation. The accompanying tinnitus was reduced or disappeared entirely. Improvement was noted in 11 of the 13 cases operated upon, and especially marked in 8. He admitted, however, that only time could testify as to the permanence of the results. Howarth,⁶ however, reported failure in all 7 cases operated upon by himself, although he learned the technique by personally working with Holmgren. It was apparent that most failures with the techniques described were due to the closure of the surgical fenestrae by bony callus or regeneration. Lempert⁷ in an outstanding contribution to the surgical treatment of otosclerotic deafness, described his method of obtaining a permanent fistula of the labyrinth that mechanically prevents bone regeneration at the site of the fenestration. In a brilliantly planned procedure, he effects a trough-shaped opening in the external semicircular canal and maintains the mobility of the labyrinthine perilymph by replacing the removed bony capsule with a durable tissue derived from the tympanic membrane and the skin of the external meatus. The entire procedure is performed in one stage, through his endaural or meatal approach. This incision within the external auditory canal obviates a postauricular scar and gives a better cosmetic result. With painstaking postoperative audiometric controls, the surgical fenestra has remained patent in 22 of his 23 cases, with good practical improvement of hearing in 19 and failure in 4. While the high degree of technical skill and minute knowledge of the anatomy of the temporal bone, necessary for the proper execution of this procedure, will prevent in some degree its universal adoption, it offers more for the unfortunate otosclerotic than anything we have today.

No review of the advances in the treatment of otosclerotic deafness would be complete without reference to the modern types of hearing aids that have been developed. This phase of the subject has been masterfully presented by Hayden,⁴ who describes the fundamental features of the newer types of electrical hearing aids. These are mainly instruments that utilize a small electronic tube and associated electrical circuits. By varying the electrical and certain mechanical constants of the instruments it may be made to amplify especially in the low, middle or high registers. Instead of a nondescript hearing apparatus the physician may now prescribe an instrument that amplifies mainly those tones that the patient perceives least well. With an audiogram a definite graph of the patient's hearing is obtained throughout the audible range; then varying the constants of the hearing aid, one can make it amplify mainly in the area that shows the greatest depression in the audiogram. In other words, the aid is fitted to the patient's individual defect. The use of such selective amplification in hearing aids is a definite trend in the direction of scientific prescription of hearing aids, rather than the older one of trial and error.

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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STATUS OF CHEMOTHERAPY IN SCHIZOPHRENIC AND AFFECTIVE REACTIONS.

THIS review deals primarily with the history, pharmacology and chemistry, pathology, selection of cases, technique, complications, results and theory of metrazol shock therapy as it is employed in the treatment of schizophrenic and affective reactions. The present trend in insulin therapy is noted, as well as experimental work with triazol, nitrogen-oxygen mixtures, pure nitrous oxide and coriamyrtin. The rôle of these agents in relation to the larger problem of treatment in psychiatry is discussed.

Psychotherapy⁵³ is primarily concerned with the study of individual personality structures and bringing about such changes as are necessary to enable the patient to adjust to the world as it presents itself to him. Situational changes are often a part of the program but rarely a major one. At the present time the personality disturbance in the great majority of mental hospital admissions had already advanced to a point of disorganization such that these patients are not readily accessible to the most productive psychiatric approaches. This is undoubtedly a factor in the duration and chronicity of schizophrenic and affective illnesses. These disorders account for from 50 to 80 % of the population of our mental hospitals today; one-fifth of all the hospital beds in the United States being occupied by schizophrenic patients alone.²⁴

For centuries the mentally ill have been plied with every variety of device and chemical in attempts to "cure" them. Of more recent years psychiatrists have been interested in the use of agents which might assist disorganized and inaccessible individuals to achieve the degree of integration necessary to permit an application of personality and situational therapies. One of the most important of these developments, the insulin shock treatment of Sakel,⁴⁷ was reviewed in these

columns in December, 1937.²⁵ Within the last year the popularity and application of this form of treatment has very notably declined chiefly due to the advent of metrazol and other therapies which are simpler, much more economical, less time consuming and thought to yield equally good results.³⁶ Recurrences of illness in insulin treated patients have also been a disturbing factor.^{23,59} In our own experience, 10 of 41 patients discharged to society have returned with recurrences within 1 to 27 months.

Pentamethylenetetrazol (cardiazol or metrazol¹) was first prepared by Schmidt^{49,50} in Germany in 1925 as a result of efforts to synthesize the active agent in camphor in soluble form. Although some physicians⁴⁸ still use the drug as a cardiorespiratory stimulant, laboratory and clinical studies have failed to establish its value in this connection.⁴ L. von Meduna³⁴ of Budapest in 1935 was the first to report upon administration of the drug in convulsive doses to schizophrenic patients. The treatment was used because of his conviction that epilepsy and schizophrenia were biologically antagonistic. This conviction was based upon theoretical, pathological and clinical evidence.

His tenets were that the characteristic habitus in epileptics was pyknic with a tendency to mesodermal overdevelopment while schizophrenics more often were asthenic with poorly developed mesodermal elements. The glial system in epileptics was thought to be hyperplastic while that in schizophrenics was considered hypoplastic. Telatin's⁵⁵ conclusion that carbohydrate metabolism was delayed in schizophrenics and accelerated in epilepsy was also cited. Nyiro³⁹ in 1929 reported that the spontaneous recovery rate in epileptics with schizophrenia was ten times that in uncomplicated epilepsy. Müller,³⁷ a year later, suggested that this fact might be therapeutically useful but did not follow it. Steiner and Strauss⁵² went so far as to state that the rarity of combined epilepsy and schizophrenia is such as to justify a question of such a diagnosis, while Mayer-Gross³² stated, "up to the present no real combination of schizophrenia with genuine epilepsy has been described."

After some laboratory and clinical experiments utilizing intramuscular camphor in oil as a convulsant, Meduna dropped this substance because the injections were very painful and responses delayed and uncertain. Burrows³⁸ observation of 1828 is of interest in this connection: "In a case of insanity, where two scruples (of camphor) were exhibited, it produced a fit, and a perfect cure followed." Meduna then settled upon the intravenous use of metrazol as a convulsant and developed a technique of administration which has been adopted generally. So popular has this approach become that in less than 4 years over 300 papers concerning it have appeared in the domestic and foreign literature.^{34c} The drug metrazol comes as a white crystalline powder, heat stable and freely soluble in water, the pH of its solutions being compatible with body fluids.¹⁰

Pharmacologically, Camp⁹ found that it had no effect on the normal heart, that it produced convulsions by medullary action, that through its central action on autonomic centers a mixed sympathetic and parasympathetic picture results, and that laboratory evidence makes clinical application questionable. Whitehead⁵⁷ pointed out that immediately after administration of the drug a fall in

blood pressure occurs and cautioned against its use in shock. Quinidine shock induced in animals and patients by Barker and Levine⁴ was made worse by metrazol, also (the drug) "did not have any beneficial effect on the cardio-respiratory mechanism." Respiratory paralysis induced by sodium amytal was in no way helped by metrazol in the laboratory of Rice and Isenberger.⁴⁴ David and Vareed¹⁰ observed that metrazol convulsions in animals are caused by action on the medulla and spinal cord and that its actions are not consistent or constant.

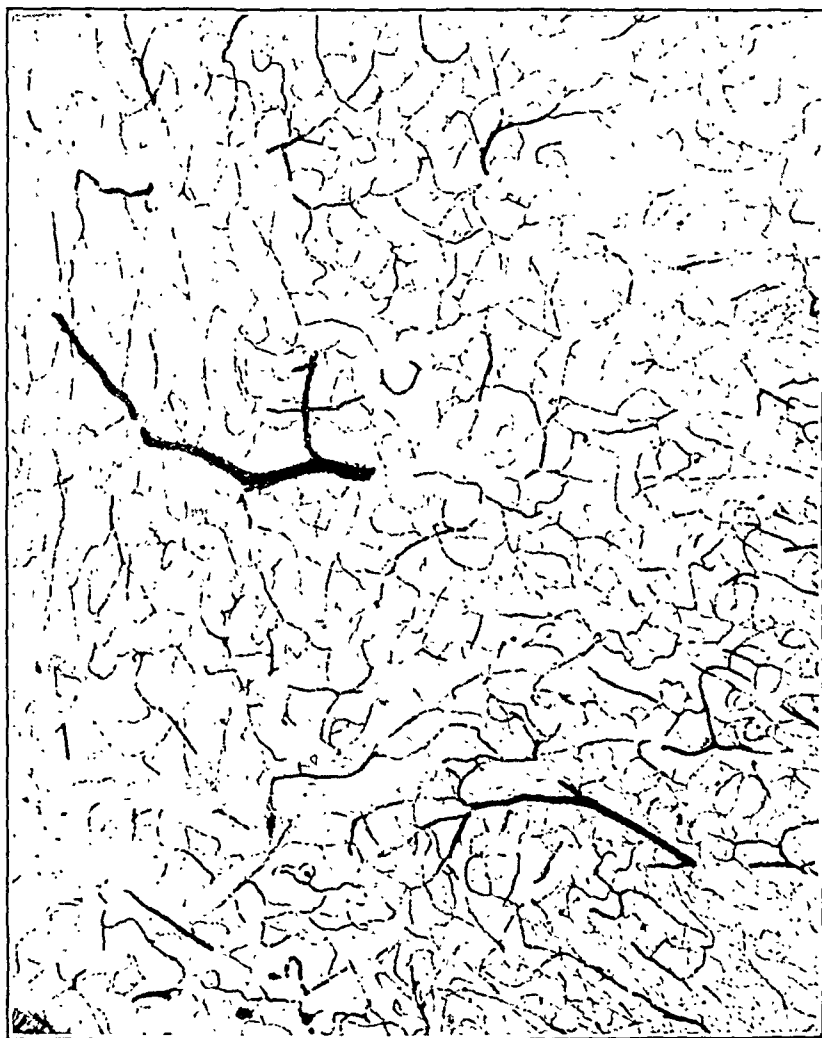


FIG. 1.—The cortical capillaries during metrazol poisoning (benzidine stain).

The main pathologic findings in animals receiving lethal doses of metrazol consist in massive engorgement of all abdominal viscera and dilatation of abdominal vessels.⁹ Neuberger³⁸ has examined dogs decapitated during metrazol convulsions and gives the following as a preliminary report:

"The cortex on application of benzidine stain (Fig. 1) shows a very irregular blood supply. There are widespread anemic zones; the blood content of the capillary network appears not in continuous columns but in broken segments suggesting a marked circulation disturbance with diminished blood flow through these regions. From observations to date no characteristic or irreversible cell changes have been noted.

"These findings are similar to those of Dreszer and Scholz¹² in the brains of cats sacrificed in various stages of metrazol convulsions." Esser and Kühn¹⁶ examined the body of a person who committed suicide with metrazol and found that the brain was hyperemic with beginning thrombotic processes, the glia and ganglion cells being apparently unaffected. It is thus apparent that from present knowledge one could not prognosticate permanent physical or brain damage from exhibition of the drug.

As with any therapeutic research, diagnostic criteria and complete examinations on all treated cases are important in the selection of material. We do not give the drug to any patient who is accessible to other less drastic therapeutic procedures. Granted a positive diagnosis of a schizophrenic reaction, young physically healthy individuals who have been psychotic less than 6 months or a year stand to benefit the most. Remission rates in schizophrenic illness present longer than 18 months drop off rapidly so that it is inadvisable to treat cases of more than 3 years' duration.²⁸ Beckenstein⁵ has pointed out that the degree of regression present might serve as a better prognostic index than duration of illness. Most clinics do not treat patients above age 40 or 45 or those with renal, cardiovascular, hepatic or tuberculous manifestations.³⁵ When any chronic illness exists such a case is considered on its own merits but no febrile or acutely ill patient is given this treatment.

Some depressive patients as old as 65 or 70 have been treated without untoward difficulty⁶ but this practice may well result in damaging mortality if too freely observed. Simple and hebephrenic types of reaction do not benefit as notably as catatonic and paranoid ones.³⁵ All types of depressive patients are fit candidates if ordinary approaches fail after fair trial. Manic reactions are being treated on a purely experimental basis and with encouraging results.^{28,35} Detailed medical and psychiatric histories are secured from all patients as well as outside sources, followed by careful mental status examination and thinking disorder tests. Physical and neurological examinations are supplemented by routine blood studies, cytological and chemical, and Roentgen ray of spine and chest as well as electrocardiogram. All patients should be hospitalized in the care of psychiatrists competent to conduct proper psychotherapy concomitant with and following treatment.

The drug is prepared in 10 % solution and is given three mornings per week. Breakfast is deferred on these days. No sedatives are given *the night preceding treatment* because in general they tend to prevent convulsive responses. When sedation is imperative paraldehyde is preferred. Friedmann^{18b} has advocated large doses of soda with the idea that the convulsive threshold would thereby be lowered. This assumption has recently been refuted by the carefully controlled study by Dean.¹¹ The solution is given intravenously through a size 18 needle and injected as rapidly as possible because a convulsive response depends

upon an immediate high concentration of the drug in the blood stream and the body disposes of metrazol very quickly. No relationship between body weight, age or sex and convulsive threshold has been observed. Female patients are ordinarily started on 3 to 4 cc. and males on 4 to 5 cc. of the drug. If no seizure results, another injection is given 10 minutes later and the quantity increased 0.5 to 1 cc.—the feeling being that a response must be secured each treatment morning to avoid the marked anxiety and agitation which often occur if no convulsion is induced.

In general, this therapy is not relished by patients, it being necessary at times to use force in administering it. The tension and anxiety which often appear between and before treatments are disturbing factors, but Meduna and Friedman³⁵ have pointed out that they may be of importance in bringing about improvement. Treatment may be given in a special screened treatment ward or in a room reserved for this purpose and patients then removed to their beds via litter. No patient is permitted to observe another during or after convulsive response and the words "fits," "convulsion" and "seizure" are never used in the presence of a patient. An oxygen tank and ample quantities of caffeine, adrenalin, ephedrine and sodium amytal are always readily available. A specially trained nurse notes vital signs and spontaneous productions of the patient, times the phases of response, and records blood pressure, autonomic responses and neurological findings observed by the physician. No attempt is made to restrain convulsive movements. One orderly prevents the mouth from opening too widely, as this contributes to dislocations of the mandible, and inserts a gag, consisting of tongue blades covered with gauze or of a cylinder of absorbent material, far back between the molars. Another orderly manages the extremities, keeping the upper arms adducted against the chest and not permitting the legs to cross, or an acute antifixion of the vertebral column to occur since these measures markedly reduce osseous complications.

After some experience one learns that the exact reaction to a given dose of metrazol in a given patient cannot be predicted. He knows that some grouping of the phenomena represented in a number of possible findings will occur. Earlier workers divided reactions into: 1, psychological; 2, abortive, 3, epileptiform.³ Psychological and abortive reactions result only when insufficient drug is given to produce a true convulsion. Contrary to popular opinion, the metrazol convulsion is not a typical grand mal seizure, since it usually consists of three phases and there is no frothing at the mouth, usually no aura is experienced, the mouth is widely opened during the tonic phase and the characteristic post-convulsive somnolence and irritability are not noted.²⁸

The latent period following injections of the drug and the convulsive response is usually between 10 and 20 seconds. One instance has been noted in which a convulsion followed administration of metrazol by 20 minutes¹⁴ and we know of an instance in which a convulsion followed after 5 days in a non-epileptic patient. Cough occurs in less than $\frac{1}{2}$ of the patients and when it does occur follows injection of the drug by a few seconds. Blinking and minimal twitching of the facial muscles are the commonest early signs noted. These may be followed in a few seconds by a short generalized clonic phase lasting 5 to 15 seconds and

followed by a tonic phase of 5 to 30 seconds. The tonic phase is accompanied by a cry in a fair proportion of cases; during this phase the mouth is invariably opened widely permitting insertion of a gag. The tonic position is usually opisthotonos, occasionally enopisthotonos, with the arms and legs extended, the feet inverted, the fingers flexed, the thumb in the palm, the eyes tightly closed. Some tonic phases are not preceded by a clonic phase. Often a bright vasomotor flush extending from the face downward, in some cases as far as the abdomen accompanies this phase. Ejaculation is quite common during this phase. Then follows a clonic phase characterized at first by short rhythmic clonic movements which with each movement increase in amplitude and last from 15 to 30 seconds, thus making the total convulsion occupy 25 to 75 seconds.

During the final clonic phase the color usually becomes quite cyanotic and not infrequently presents the leaden appearance of anoxemia. The final clonic phase is usually followed by a period of apnoea varying from 5 to 15 seconds, while some patients at once resume breathing either of a loud stertorous nature or, at first, with only short shallow movements. In right handed individuals the eyes usually rotate far to the left by the end of the tonic phase and then swing back into a forward gaze a few seconds following the final clonic phase. Immediately following the injection of the drug the pupils usually dilate quite widely for a few seconds, return to normal size throughout the seizure and again dilate quite widely from 5 to 30 seconds after the clonic phase to remain thus up to 30 minutes. The pupils are fixed to light during the seizure but become sluggishly responsive 2 to 5 minutes later. Oversalivation is frequently noted during the convulsion. The pulse is usually between 90 and 120 following the convulsion—in some instances it is as slow as 60. The average patient is somewhat restless for a few minutes following the seizure, necessitating constant attendance to insure against falling out of bed. An occasional patient becomes so hyperactive at this time that 3 or 4 persons are needed to keep him in bed. Such periods are always shortlived. Subjects remain acutely confused and stuporous from 5 minutes to 2 hours and present an amnesia dating from the moment of injection. In some instances, a retrograde amnesia extending back 2 or 3 hours is met with. Some patients present what we have termed "secondary" reactions from 1 to 5 minutes after the convulsion has passed.²⁸ These usually consist in a few abortive clonic movements. Perspiration is often noted and is greatest after the seizure has occurred. Urinary incontinence during the seizure, we find, is not common.

The commonest post-convulsive neurological finding is bilateral ankle cloni without confirmatories. Patellar cloni are uncommon. Babinski and Chaddock signs occur in about 1 patient out of 10. A positive Hoffman sign is not unusual. The commonest subjective sensation following injection is one of "fainting away—like going under an anesthetic." Common post-convulsive complaints are those of muscle soreness, backache, headache, dizziness, difficulty in thinking, nausea, and extrasystoles. Some patients become quite alarmed because of extrasystoles and require reassurance as to their cardiac status. An occasional person complains of precordial pain; if a repeat electrocardiogram is normal treatment is continued. Post-convulsive vomiting

is not unusual and may recur several times during the morning but by lunch time patients are almost always hungry and retain food. Notable increase in appetite and gain in weight coincide with psychiatric improvement in a good percentage of cases.

Following a convulsion patients are kept in bed and closely observed from 1 to 3 hours. They take part in all routine afternoon ward activity.

Although the mortality reported to date from this therapy is less than 1% in well chosen and managed cases³⁵ one should bear in mind the possibility of minor or major complications and sequelæ both at the time of treatment and remotely afterwards. In animals, the lethal dose of metrazol is $1\frac{1}{4}$ to $1\frac{1}{2}$ times the convulsive dose,⁹ so it is best to follow the conservative policy of beginning with small doses and increasing slowly.

In addition to the common complaints noted above, other complications are dislocations and fractures resultant upon the excessive muscular activity during the convulsion. The mandible is occasionally dislocated when the mouth is opened too widely¹³ during the tonic phase. Anterior dislocation at the shoulder joint is less often met with. Once this has occurred and the head of the humerus replaced future dislocations are avoided by strapping the arm on the affected side so that the palm of the hand rests upon the opposite clavicle. Fractures of the humerus and femur have been reported but are not common. Polatin⁴⁰ and others at the New York Psychiatric Institute have reported vertebral fractures in over half of the patients treated by metrazol. This incidence of such a serious complication, if established, would dampen the enthusiasm of most workers for the treatment. We have studied 25 post-treatment cases in this clinic and found no vertebral lesions that could be positively attributed to the treatment and only 2 questionable cases.

Two deaths have been reported due to pulmonary emboli which may have originated as thrombi in veins injected with metrazol. This source of difficulty is minimized by keeping a record of the vein used each time and not using this vessel again for at least a week, thus allowing time for at least partial organization of any possible thrombus.²⁶ Beckenstein⁵ reports 6 cases of lung abscess, 4 cases of pneumonia and a state similar to status epilepticus in 218 patients treated by him.

Clinical reports give no advice as to measures to be taken when a patient presents shock or fails to respond following a convulsion. Experimental work would indicate that CO₂ and oxygen, adrenalin and caffeine are the drugs of choice.

The ordinary treatment course comprises 15 to 30 convulsions. Remissions have appeared after as few as 2 or 3 injections. We continue treatment as long as increasing improvement is observed and usually give 2 to 4 injections after a satisfactory remission or plateau has been reached.

Any consideration of treatment results in schizophrenia must take into account the fact that spontaneous remissions occur in from 10 to 30% of untreated cases.⁴⁵ Reliable data with adequate follow-up study of cases is not available. A recent study by Fromenty indicates that eventually 85% of all schizophrenic patients develop a permanent psychosis.

The validity and uniformity of diagnostic criteria must be evaluated in any attempt to compare results secured in various clinics and in various countries. A classification which places patients considered as manic-depressive reactions in one clinic in the schizophrenic group in another clinic obviously does not provide a basis for comparing statistics from the two clinics.⁷

Another important consideration in evaluating results is the need to measure the quality of remission achieved. Since this was pointed out in 1937 by Rymer, Benjamin and Ebaugh⁴⁶ no reported study has yet included it.

Most clinics are classifying results according to the criteria of Sakel,^{47d} who defines a complete remission as present when the patient is free of all symptoms, presents a normal affect, has insight into his illness and is able to return to his former work. An incomplete remission is achieved when the individual is symptom free but defective in one of the other points noted. When the patient remains ill but is able to work in society he is considered a social remission.

von Meduna's^{34c} first 110 patients resulted in 54 remissions and 56 unchanged. A deluge of reports on treatment results in various clinics and countries has appeared in the last 1½ years. Reitmann⁴² recently presented a summary of reports from 7 countries. He found difficulty in his task because of lack of uniformity of criteria used in evaluating remissions and differences in psychotherapy, method and number of shocks given. Of 2011 cases reported 840 were of less than 18 months' duration. Calling these cases "acute and subacute" he presents the following table:

Country.	Total.	Cases. Acute and subacute.	Full remissions.
Austria	130	64	32 (50%)
England	71	31	13 (41%)
Germany	310	129	51 (39%)
Hungary	433	178	94 (53%)
Italy	120	53	42 (79%)
Switzerland	162	51	22 (43%)
United States	785	334	183 (54%)
Total	2011	840	437 (52%)

von Meduna and Friedmann³⁵ have recently summarized over 3000 treated cases with data supplied by 75 clinics with results consistent with the above.

Results of treatment in our clinic are comparable, as shown on p. 870.

Bennett⁶ reports that all of 21 severe depressive reactions were markedly improved within 2 weeks after treatment began. One of these individuals was 65 years old. Thirteen recoveries in 16 manic-depressive cases were reported by Low²⁸ who felt that duration of affective illness was of no importance in considering prognosis with convulsive therapy. Wahlmann⁵⁶ has found results better with depressives than schizophrenics. Marked improvement appeared in all of 6 depressive patients treated by Menninger.³⁶ In our table noted above very satisfactory results in both manic and depressive illnesses are evident.

Since this therapy is of recent development the permanency of remissions cannot be determined at present, but will probably be re-

lated to individual prognostic factors and the adequacy of psychiatric management given after remission is achieved.

COLORADO PSYCHOPATHIC HOSPITAL RESULTS OF METRAZOL TREATMENT AS OF APRIL 1, 1939.

Diagnosis.	Total.	Condition.				Recurrence.
		Complete remission.	Incomplete remission.	Social recovery.	Unimproved.	
Schizophrenia	83	2	29	21	20	11 (4 committed)
Hebephrenic	8	1	1	1	5	0
Catatonic	13	0	1	7	4	1
Simple	17	0	10	4	1	2 (1 committed)
Paranoid	34	1	12	6	8	7 (2 committed)
Mixed	11	0	5	3	2	1 (committed)
Manic depressive	24	5	11	5	1	2 (committed)
Manic	5	1	3	1	0	0
Depression	19	4	8	4	1	2 (committed)
Unclassified	1	0	0	1	0	0
Total complete courses	108	7	40	27	21	13

62% of all completely treated schizophrenics still in society without any recurrence after 1 to 17 months.

100% of all completely treated manics still in society without any recurrence after 1 to 17 months.

84% of all completely treated depressives still in society without any recurrence after 1 to 17 months.

Many ideas have been advanced as to the mechanism by which metrazol brings about the results reported above. Of interest is the fact that no reports of improvement with metrazol therapy without convulsions have appeared, thus implying that the convulsion or some concomitant of it is of fundamental importance. von Meduna's biological antagonism theory has been disputed by several workers. Esser¹⁵ thoroughly reviewed the literature on incidence and described 11 cases in which epileptiform seizures occurred in schizophrenic patients. Upon statistical, therapeutic and clinical evidence Gibbs, Gibbs, and Lennox²¹ concluded that any relationship between epilepsy and schizophrenia is positive rather than negative. They add, "the electroencephalogram record obtained in patients having psychomotor seizures is similar to that seen in most patients diagnosed as having schizophrenia."

Reese, Vander Veer and Wedge⁴¹ venture that, "metrazol convulsions increase the strength of the forces of repression and push the psychosis out of consciousness." Many have felt that the death threat incident to the convulsion might explain the return to personality adjustment on a reality basis. Anygal² believes that metrazol produces an ischemia in vulnerable cortical areas, followed by hyperemia and a stimulation of affected ganglion cells. Several workers have tied their theories of the mechanism of improvement with the very controversial and involved physiological and anatomical theory of the etiology of schizophrenia and with physiological observations upon shocked patients. Gellhorn¹⁹ considers the improvement "in essence due to nothing other than strong and lasting excitation of the sympathetic division of the autonomic system, involving profound alteration in the metabolism of the brain. . . ."

Friedmann,^{18a,b} who introduced the convulsive treatment in America, postulates, "a functional barrier to facile absorption or assimilation of nutritive elements set up in the brain," and then theorizes that metrazol attacks this barrier. In another publication he offers the explanation that metrazol may become chemically attached to fixed or cell-bound toxins and thus remove them from the body.

The critical observer will not find any of these explanations valid since not one is based upon generally accepted and demonstrable fact. Few psychiatrists would grant the validity of Gellhorn's wholly organic approach or Friedman's idea that toxins are important etiologic agents in schizophrenia. One must be very cautious in accepting conclusions based upon physiological evidence in any psychiatric illness or treatment since such findings as may be observed are often unintelligible without taking into account the total functioning personality in its environment, *c. g.*, the most elaborate physiological studies upon an apparently comatose individual would be of no value in understanding his condition compared with the revelation that 1 minute earlier he had learned of an unexpected death in the family or experienced some equally adequate psychogenic shock.

In passing, it is hardly necessary to deplore the widespread circulation in the lay press of such ideas as the one that shock therapies peel off layers of cortex as one might remove layers of an onion, appearing under the names of authorities in neurology, experimental medicine and psychology.⁵⁸ Blatant headlines about "shock that cures," "brain shaking," and "new mental disease cure" appearing in magazines with authoritative sounding names,^{51a,b,c} have frightened many patients and contributed to popular misinformation.

That metrazol has no specific affect *per se* is shown by the fact that other convulsant drugs will likewise bring about improvement in these illnesses. Mayer-Gross and Walk³³ have treated 33 patients with 4-cyclohexyl 3-ethyl 1-2-4 triazol with results comparable to those achieved by metrazol and without some of the disadvantages of the latter drug.

By having subjects consume the oxygen from an oxygen-nitrogen mixture in a closed system and by not adding new oxygen, Himwich, Alexander and Lipetz,²² induced anoxemia in 5 schizophrenics, with encouraging results. This was done on the theory that decreased cerebral metabolism is the common factor in all shock therapies. This theory is based upon observations of these workers and reference to other physiological studies upon insulin and metrazol reactions during treatment.^{20,27,31} At the present time we are experimenting with this technique but by having patients breathe pure nitrous oxide until a profound anoxemia is induced. Results are slightly encouraging but not comparable to those achieved by convulsants.

In addition, we are treating schizophrenic and affective illnesses with coriamyrtin,^{13,17,29,54*} a convulsant highly toxic glucoside first described by Riban⁴³ in 1863. Experience to date indicates that this agent too will bring about results comparable to metrazol.

In conclusion, the purely experimental aspect of all these therapies is emphasized. They should only be carried out in centers where adequate psychiatric, laboratory, consultatory and follow-up facilities

* Drug supplied for experimental purpose, by Eli Lilly & Co., Indianapolis, Indiana.

are available. No matter how effective they become they will never obviate the necessity of study aimed at understanding and treating psychiatric illnesses as personality dysfunctions utilizing the ever growing body of psychotherapeutic armamentaria at the command of trained psychiatrists.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 17, 1939

The Ultra-violet Irradiation of Auto-transfused Human Blood; Studies in Oxygen Absorption Values. G. MILEY (Department of Clinical Pharmacology, Hahnemann Medical College of Philadelphia). The effects of 97 ultra-violet irradiations of auto-transfused blood by the Knott technique, in various pathologic states, including allergy, arthritis, and sepsis, on combined oxygen values of venous blood (196 determinations) were studied.

The determinations are divided into three groups:

Group 1, in which combined oxygen values, taken just before irradiations of auto-transfusions, are compared with those taken within 10 minutes following irradiations, shows that in a series of 83 irradiated auto-transfusions, there was an average combined oxygen value of 7.0 vol. % before irradiation and a combined oxygen value of 11.1 vols. % after irradiation, an average increase of 4.1 vol. % or a 58.6% gain over the original values. The greatest rise in Group 1 was from 1.0 to 8.2 vols. % and the greatest fall from 13.6 to 11.2 vols. %.

In Group 2, values were obtained in a series of 14 irradiated auto-transfusions before irradiation and $\frac{1}{2}$ hour later. These show an average combined oxygen value of 9.7 vols. % before irradiation and of 8.8 vols. % after irradiation, an average decrease of 0.9 vol. %, thus an average fall in value of 9.2%. The greatest rise was from 2.0 to 6.5 vols. %, the greatest fall from 15.0 to 9.2 vols. %.

In Group 3, combined oxygen values were obtained in a series of 27 irradiated auto-transfusions. The average before irradiation was 5.8 vols. % and 1 month or more later was 8.7 vols. %, an average increase of 2.9 vols. % or 50% over the original value. The greatest gain was from 3.0 to 17.9 vols. %, the greatest drop from 6.6 to 4.6 vols. %.

Correlation Between the Secretion of Dyestuffs by the Kidney and the Molecular Structure of These Dyes. RUDOLF HÖBER and PRISCILLA M. BRISCOE (Laboratory of Physiology, University of Pennsylvania.) The isolated frog kidney is perfused through the aorta with Ringer's solution, through the renal portal vein with Ringer plus

0.0005% dyestuff. About 30 dyestuffs have been tested. Each of them is a diffusible monoazosulphonic acid. The following conclusions have been reached: only dyestuffs displaying a distinct polar-non-polar configuration are secreted. This configuration is mainly based upon the location of the sulphonate groups. If one-half of the molecule carries one or two sulphonate groups, while the other half does not, secretory transport takes place. If one of two sulphonates is located in one-half, the second in the other half of the molecule, no secretion is observed. This has been found with 12 benzene-azo-naphthalene-mono- and di-sulphonates and with 8 naphthalene-azo-naphthalene-di-sulphonates. It is suggested that secretion occurs when $\frac{1}{2}$ of the molecule, being non-polar organophilic, is able to attach to the cell surface and the other half, being polar hydrophilic, has an affinity for its aqueous surroundings. A greater number of sulphonate radicals, even irregularly disposed in both halves, seems to strengthen the affinity to water so much that anchorage to the cell is prevented.

The Probable Relation of the Anterior Pituitary to the Diabetic Traits in a Strain of Rats. V. V. COLE and B. K. HARNED (Laboratory of Pharmacology, Woman's Medical College of Pennsylvania). Using as the criteria differences in: 1, fasting blood sugar; 2, glucose tolerance; 3, rate of growth; 4, volume of urine per unit of body weight; 5, percentage of body fat; 6, insulin tolerance, and 7, epinephrine tolerance, two colonies of *Mus norvegicus albinus*, maintained on the same diet and under the same conditions for two or more generations, gave results suggestive of a striking difference in their levels of anterior pituitary activity. The comparison of the two strains is based on data obtained from male rats paired according to age and each conclusion is supported by statistical analyses.

The stock for the colony giving evidence of the greater anterior pituitary function was obtained from the Yale Laboratory of Physiological Chemistry; but, due to our practice of mating animals from the lowest glucose tolerance range, the characteristics of the Yale strain possibly have been modified. The stock for the other colony was obtained from the Wistar Institute and all of the characteristics of that strain have been retained.

The higher fasting blood sugar and lower glucose tolerance of the Yale strain have been reported previously. Growth curves on the two strains show that the Yale rats grow faster and larger than the Wistar rats and the difference closely parallels that obtained by Evans and Simpson following the administration of anterior pituitary extracts to the Long-Evans strain.

Yale rats consume more water and excrete more urine per unit of body weight than Wistar rats. Twenty per cent of the Yale strain excreted more than 4 cc. of urine per 100 gm. of body weight per 24 hours while only 6% of the Wistar rats fell within this range. The urine was sugar free.

Up to 200 days of age the percentage of body fat of the two strains is essentially the same; however, subsequent to this period the body fat of the Yale rats increases markedly, while that of the Wistar rats

remains unchanged up to 500 days of age. The adiposity possibly is associated with changes in the gonads since an appreciable percentage of the Yale rats become infertile at 200 days of age.

The Yale strain shows a definite resistance to the hypoglycemic action of intramuscular insulin and a sensitization to subcutaneous epinephrine. The area of the epinephrine hyperglycemia produced in the Yale strain was 75% greater than that produced by comparable concentrations in the Wistar strain. These results closely parallel those obtained by Cope and Marks, and Young in rabbits treated with anterior pituitary extracts and emphasize the probability that the anterior pituitary is the deciding factor in the differences between the Yale and Wistar strains.

Cord Potentials in Spinal Shock. W. B. STEWART, J. P. HUGHES, and G. P. MCCOUCH (Laboratory of Physiology, University of Pennsylvania, and Institute of Pennsylvania Hospital). In the decerebrate cat, transection temporarily reduces the negative and almost abolishes the positive waves of the potential recorded from the dorsal surface of the cord. In the monkey, reduction of the potential is more severe and prolonged. In cat and dog, the threshold of the cord potential is usually identical with that for the ipsilateral flexor reflex, both values falling progressively after transection until they approximate that of the afferent nerve within about an hour. In the monkey, the threshold of the cord potential may approximate that of the afferent nerve within 5 hours, but reflex responses are not usually present in the acute preparation. Refractoriness of internuncials has only slightly longer duration in monkey than in cat and is similar in acute and chronic preparations. In the acutely damaged monkey, the cord potential is recordable for not more than 15 mm. above and 5 mm. below the root entrance zone. It is not recordable on the contralateral side. In the longer surviving monkey, there is recovery of the crossed internuncial potential and coincident recovery of contralateral reflex inhibition. In contrast to the case of the cat, however, there is no diminution of the cord potential of the test volley by a preceding contralateral conditioning volley. Hence the locus of crossed inhibition in the monkey appears to be at the motoneurone.

Factors Responsible for the Seasonal Incidence of Lead Poisoning in Infancy and Childhood—An Experimental Study in Rats. MILTON RAPOPORT, and MITCHELL I. RUBIN (Department of Pediatrics, University of Pennsylvania, and The Children's Hospital of Philadelphia). Frank clinical lead poisoning in infants and children—chiefly lead encephalopathy—has its greatest incidence during the late spring and summer months. An experimental elucidation of this seasonal incidence was attempted by a study of the effect of three factors upon rats poisoned with lead.

A. Heat. Exposure of rats during or after a period of lead ingestion to temperatures of 40° C. for 4 hours daily did not increase the severity of the lead poisoning.

B. Exposure to sunlight of rats ingesting lead greatly increased the severity of the lead poisoning. Similarly, administration of cod liver

oil to rats ingesting lead produced very severe lead poisoning. It is suggested that these effects are due to the increased absorption of lead from the gastro-intestinal tract produced by the vitamin D activity in sunlight or cod liver oil.

C. The photosensitizing effect of sunlight on the porphyria of lead poisoning did not seem to be of importance in rats poisoned with lead.

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